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OF

DERMATOLOGY AND SYPHILOLOGY

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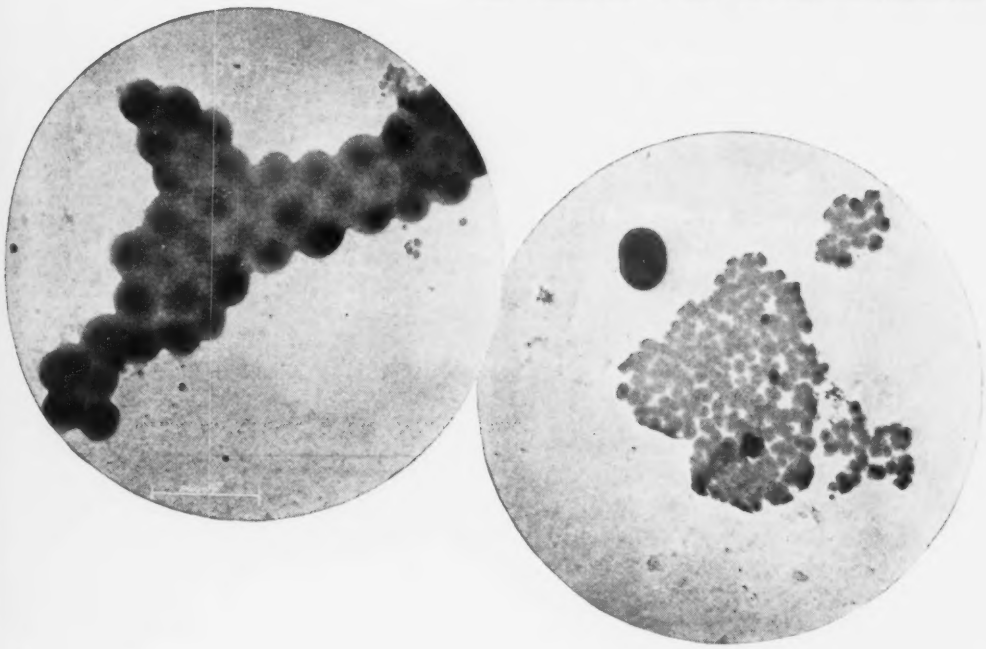

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Since cosmetics are so universally used it is not to be wondered that they sometimes figure in the field of allergy. That is why when there is a history of allergy we suggest that patch tests be made with those of our products the subject is using or contemplates using. If they test positive, further testing with their constituents is indicated to determine the offending agents. These found, we frequently can modify our formulas to suit the subject's requirements. The patch test is generally considered best for testing cosmetics because it most closely approximates the conditions under which they are normally used.

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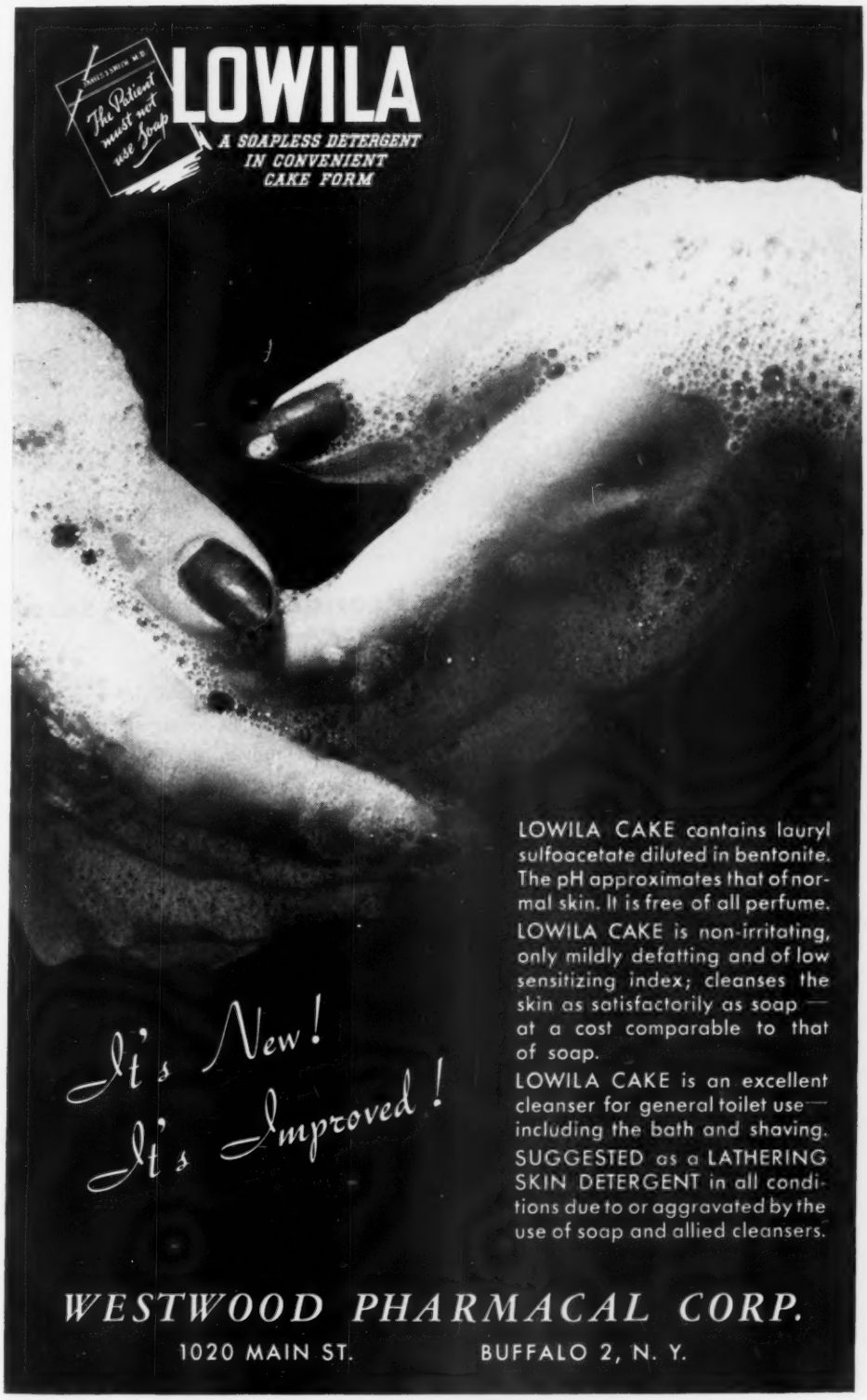

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Archives of Dermatology and Syphilology

VOLUME 51 FEBRUARY 1945 NUMBER 2

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THE ELECTRON MICROSCOPE IN DERMATOLOGY

GEORGE L. CLARK, PH.D., D.SC.; MARTHA BARNES BAYLOR, PH.D.; DOROTHY E. MARTIN, PH.D., AND GERTRUDE T. RAFFERTY, M.S.

URBANA, ILL.

One of the newest of all scientific instruments, which in only three years has a remarkable record for achievement, is the electron microscope. With it has developed an entirely new branch of physics known as electron optics. The present and the potential applications of electron optics and this powerful new instrument to the medical field of dermatology and syphilology are the subject of this brief preliminary paper. Electron micrographs obtained largely with the RCA instrument at the University of Illinois are used to illustrate the new facts of structures at high magnifications of cutaneous tissues of several kinds, individual cells and single protein molecules.

The University of Toronto, under the leadership of Prof. E. F. Burton, pioneered the development of this new science on this continent with a homemade equipment. There were only two or three other homemade installations in the United States prior to the arrival of the RCA electron microscope at the University of Illinois, just three years ago. There are now about forty of these RCA microscopes in operation in this country in the laboratories of universities, industries, hospitals and research institutions, besides other units which have been shipped abroad under Lend Lease.

A brief explanation of the theory, design, construction and operation of the electron microscope must suffice. Perhaps the most pertinent questions are why one has it and what it does that other methods or instruments cannot do. In microscopy, the concern is with resolving power, by which is meant how close together may two points be and yet appear as two separate, distinct points. The very best optical microscope available has a limiting resolving power of about 0.2 micron (1 micron = 0.001 mm.); this value may be reduced to about 0.1 micron when ultraviolet rays are used for illumination and quartz instead of glass lenses are used in the microscope. Below this limit of resolution, or size of particle which can be observed, there has been no instrument capable of delineating smaller objects or fine structures of any material, although such methods as roentgen ray and electron diffraction indirectly led to measurements of a few ten millionths of a millimeter (or ten thousandths of a micron). When it was predicted by de Broglie in 1926 and then experimentally confirmed that a beam of electrons has a wavelength, just as light has a wavelength, but many times smaller even than that of ultraviolet radiation, the essential step was made toward the construction of a microscope with one hundred times the resolving power of any existent optical microscope. In other words, two points only 0.000001 mm. apart (or 1 millimicron) should be clearly separated—and then the size and shape of particles only one one-hundredth as large as any ever before observed be revealed. In the electron microscope, therefore, a beam of electrons from a hot filament, or "gun," and accelerated by voltages up to 60,000 volts takes the place of the beam of light usually reflected into ordinary microscope barrel by a mirror; magnetic fields produced by electric current in coils, fulfil the function of lenses instead of glass or quartz. Part for part, there is an exact analogy between the optical microscope and the electron microscope. The latter, however, further requires an extremely high vacuum, since air scatters the electrons; this means that moist and living specimens cannot long exist unchanged. Furthermore, the specimens must be exceedingly thin, since electrons are far more easily stopped than is light. Thus, the glass microscope slide is replaced by a collodion film only 10 millimicrons thick, which is picked up off a water surface as an invisible film and then supported on a tiny piece of 250 mesh wire gauze. The photographs are all made through one opening of this exceedingly fine gauze. The RCA electron microscope is a marvel of electrical and mechanical engineering; control must be so nearly perfect that the

From the Department of Chemistry, University of Illinois.

Read before the Section on Dermatology and Syphilology at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 14, 1944.

electrical circuits are very complex; for example, fifty-two vacuum tubes are required. Since the velocity of the electrons determines the wavelength and this must have as nearly as possible a single value, the high tension system produces a voltage of 60,000 ± 1 volts, in itself a remarkable achievement. A direct magnification of nearly 30,000 diameters is obtained, and this image is then photographically enlarged to 100,000 to 125,000 diameters. The magnification of an image of comparable sharpness in the optical microscope is about 1,000 diameters.

the method of Cowdry. The ear was soaked for twenty-four hours in 10 per cent acetic acid. The skin was then peeled off in thin sheets, which then were either stained or mounted for optical microscopic examination or were stretched over the fine mesh screen mounting for the electron microscope. The stained preparations photographed with the optical microscope are seen in figure 1 *A* and *B*. The cell boundaries are clearly distinguished, and the nucleus appears dark owing to the stain employed. Figure 1 *C* reproduces electron micrographs made at the same

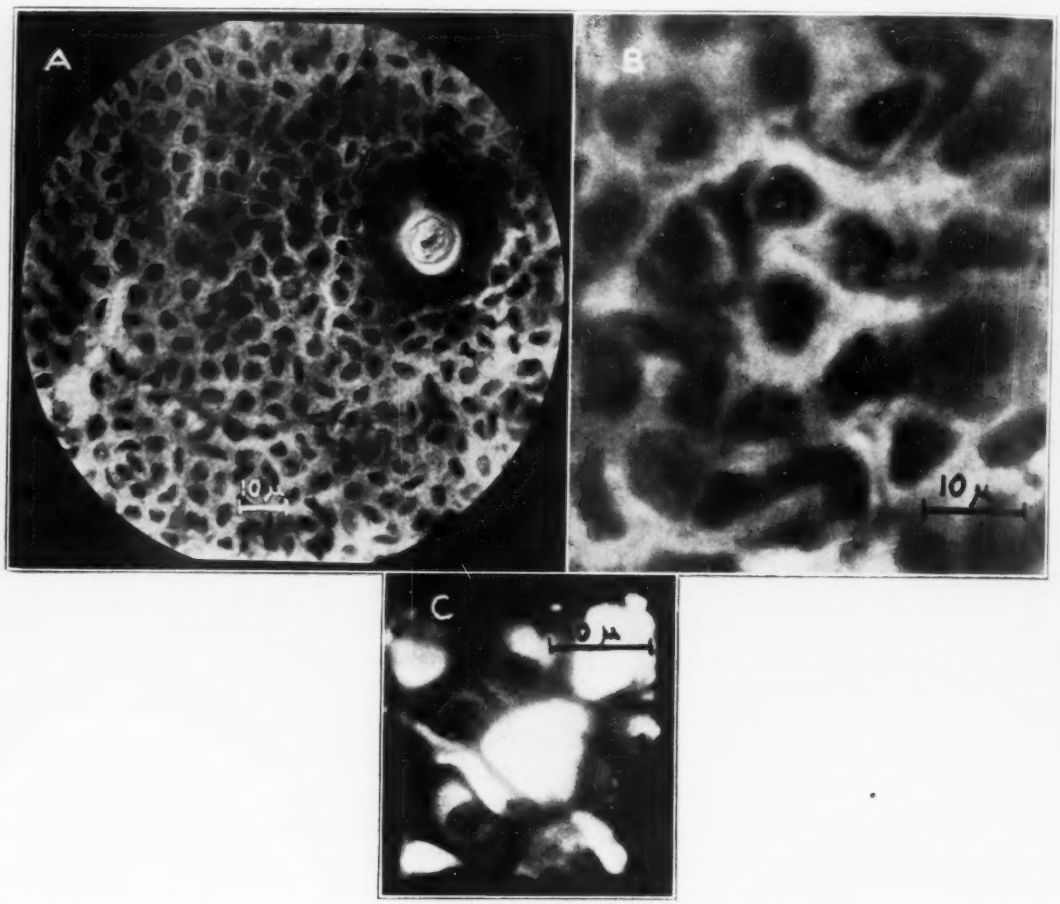

Fig. 1.—*A*, optical photomicrograph of surface layers of skin from a rat ear (480 diameters); *B*, optical photomicrograph of same preparation as in *A* at higher magnification (1,440 diameters); *C*, electron micrograph of surface layers of skin from a rat ear at the same magnification as *B* (1,440 diameters).

ELECTRON MICROGRAPHS OF SKIN

Thus far on the various electron microscopes in the United States very little work has been completed on the study of normal and pathologic skin structures, either epidermal or dermal. One of the limitations of the electron microscope is especially important in dealing with specimens of this type, namely, the extreme thinness which is required for penetration by the electron beam and for suitable resolution. The skin from the ear of an adult rat was prepared according to

magnification as the optical photomicrograph in figure 1 *B*. Again all boundaries and nuclei stand out clearly, and the detail is much sharper than that obtained with the optical microscope, thus illustrating the greater focal depth of the electron microscope. Figure 2 *A* is an enlargement of the same photograph, but here the sharpness and detail are diminished owing to the limitations of penetration. The electron beam is able to penetrate sections of 0.1 micron thickness, but the resolution diminishes as the section

becomes thicker. Figure 2 *B* is at a still higher magnification and with still poorer detail. Only the edge of the specimen can be penetrated; hence little information concerning the individual cells can be gained by this technic. Thinner sections are therefore essential if the cell is to be studied as such. At the very edges of the stretched membranes may be observed a structureless layer which is interpreted to be the thin fibers. If such regularity of structure were present in the membrane, the resolution and magnification are entirely adequate to show this. In this very preliminary and limited observation of skin structure, it is evident that net a great deal has been added to the information available from the optical microscope and that effort must now be directed to the end of preparing much thinner tangential and cross sectional specimens;

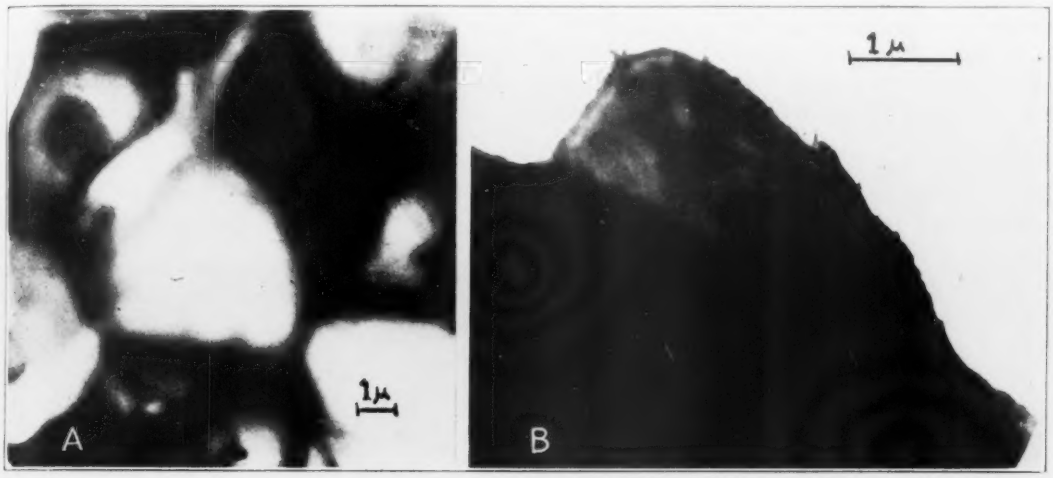

Fig. 2.—*A*, electron micrograph of same preparation as in figure 1 *C* at higher magnification, 4,300 diameters; *B*, electron micrograph of same preparation at edge, at magnification of 15,100 diameters.

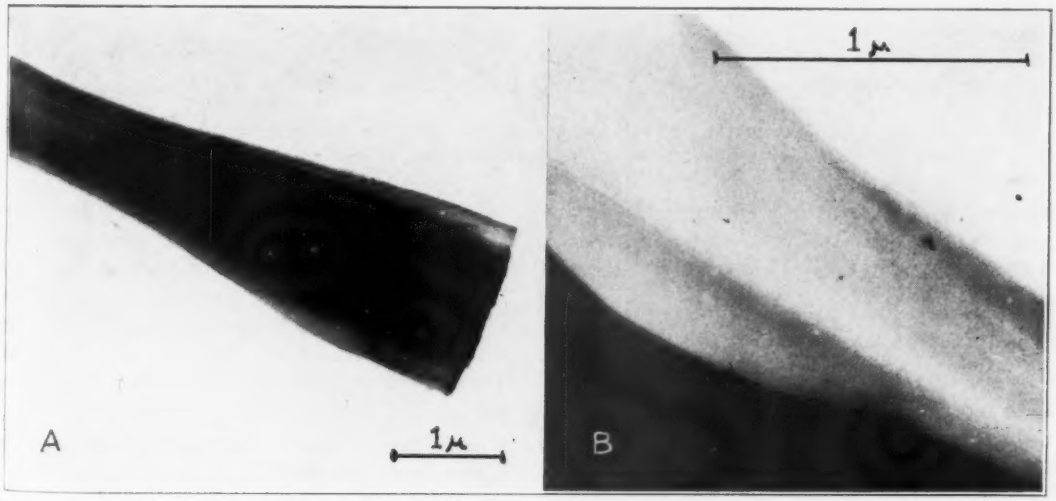

Fig. 3.—*A*, electron micrograph of thin sheet of keratinized membrane from stratum corneum (15,100 diameters); *B*, electron micrograph of thin sheet of keratinized membrane from stratum corneum curled up (43,125 diameters).

sheet of keratinized membrane from the stratum corneum. Figure 3 *B* shows at very high magnification this membrane stretched out in a sheet, while figure 3 *A* shows the same extremely thin membrane curled up like a sheet of paper. Figure 3 *B* shows none of the long spacing periodicities of about 660 angstrom units, or 66 millimicrons, previously observed in collagen

research to this end is being continued in which various methods of cutting the specimens, including those frozen, are being worked out.

ELECTRON MICROGRAPHS OF OTHER TYPES OF TISSUE

Success has already attended the efforts to study several types of animal membranes and

tissues, especially those which are laid down in the thinnest and most delicate form and hence require no additional preparation for the electron microscope. The paper presenting the results of this study will illustrate the structure of butterfly wings, single filaments of spider web, insect trachea and air sacs, mosquito egg cases, which are only 0.01 micron thick, and cockroach cuticle.[1] These photographs illustrate a remarkable design of construction, with long parallel reenforcing filaments together with cross filaments like the rungs of a rope ladder. Studies of cockroach cuticle have led principally to the study of remarkable spiral tubes, of which there are 2,500,000,000 in the cuticle of each insect. These spiral tubes terminate not in the outer cuticle surface but at some distance below. Hence, they cannot be air or liquid vents, and their function still remains a mystery. This discovery was made with the electron microscope of the University of Pennsylvania Medical School.

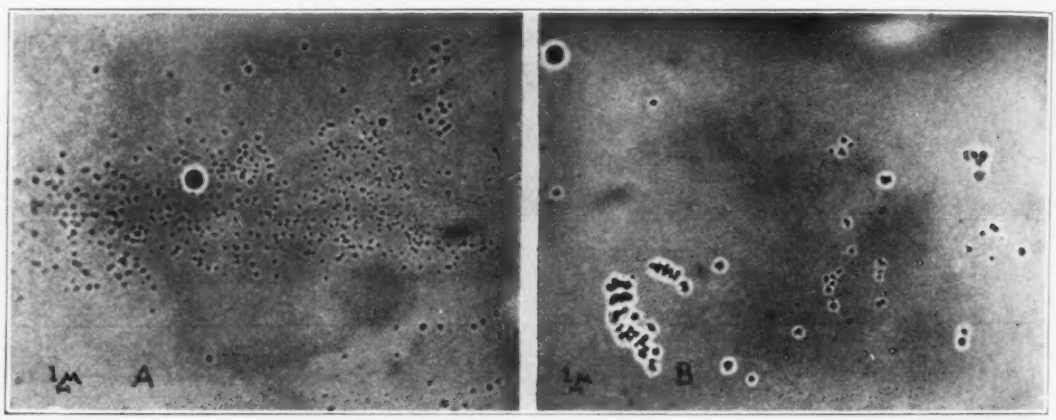

Fig. 4.—*A*, optical photomicrograph of cellular granules extracted by differential centrifugation (1,380 diameters); *B*, optical photomicrograph of cellular granules as in *A* but on another preparation.

ELECTRON MICROGRAPHIC STUDY OF CELL CONSTITUENTS

The most fundamental problem in any biologic field is, of course, the structure of the individual cells. As typical of this type of investigation, a report is made of new work on the chromosome. Claude [2] in 1942 published a technic for extraction of chromatin threads from somatic cells. The materials were chick embryo and rat liver and spleen. Grinding with pure silica at 5 C. in pure conductivity water followed by centrifugation at a force greater than 1,500 times gravity led to a preparation on the collodion film which rested on the surface of distilled water so that salts were dialyzed through the film and the protein material was left on the surface. Figure 4 consists of optical photomicrographs of the cell constituents, indicating granules of two sizes without evidence of other materials. Figure 5 *A* is an electron micrograph of these granules (which give a positive Feulgen reaction and must be nucleoproteins of the desoxyribose type) together with albuminous unoriented masses, similar in appearance to dried egg albumin, and most interesting distinctly fibrous masses (fig. 5 *B*) which spray out into individual fibrils (fig. 5 *C* and *D*).[3] The diameters of the smaller fibrils in figure 5 *D* are of the order of 0.025 microns. As further proof of the nucleoprotein nature and the chromosome origin, these materials were found to have the typical ultraviolet absorption at 2,600 angstrom units and the solubility in molar solution of sodium chloride and reprecipitation at 0.15 molar solution of sodium chloride, as found by Mersky and Pollister.[4] These photographs seem convincing evidence of the fibrillar nature of the chromosome.

Evidence of the axial fibrillar structure of sperm (bull and chicken) is shown in remarkably beautiful electron micrographs.[5] Especially significant is the fact that the tails spray out into ten fibrils.

1. Richards, A. G., Jr., and Anderson, T. F.: Electron Microscope Studies of Insect Cuticle, with a Discussion of the Application of Electron Optics to This Problem, J. Morphol. **71**:135-183, 1942.

2. Claude, A., and Potter, J. S.: Isolation of Chromatin Threads from the Resting Nucleus of Leukemic Cells, J. Exper. Med. **77**:345-354, 1943.

3. A similar electron micrograph is provided by macerated actinomycotic granules, provided by Dr. J. H. Lamb, Oklahoma City. These results will be published in detail later.

4. Mersky, A. E., and Pollister, A. W.: Nucleoproteins of Cell Nuclear, Biol. Symposia **10**:247-261, 1943.

5. Baylor, M. R. B.; Nalbandov, A., and Clark, G. L.: Electron Microscope Study of Sperm, Proc. Soc. Exper. Biol. & Med. **54**:229-232, 1943.

ELECTRON MICROGRAPHS OF SINGLE PROTEIN MOLECULES AND VIRUSES

This laboratory has been fortunate in its excellent results in this field.[6] Several hundred measurements on electron micrographs of single molecules of Loligo peali (squid) hemocyanin yield an average value of 8.0 millimicrons for the diameter of the particles, which seem to be spherical. The molecular weight calculated is 216,000, which is exactly eight times the unit structural protein value of 27,000. Limulus (king crab) hemocyanin has the diameter 17 millimicrons. Influenza virus particles have been measured several times and found to have a value of about 10 millimicrons. The bacteriophage of Salmonella pullorum has just been studied in this laboratory.[7] The size is 40 to 45 millimicrons. The characteristic lysis of the bacteria is clearly shown, but in the course of the research a new phenomenon was observed. This is an agglomeration into microcolonies of the virus particles on the edges of bacteria which do not undergo destruction. This appears to be a defense mechanism set up by the bacteria to resist lysis. Cultures inoculated with lysate of disintegrated bacteria seem to have this flocculating and resisting power. In contrast, photographs will be shown of bacteriostasis with penicillin. The spirochete of syphilis with its flagella, photographed in several laboratories, will also be illustrated.

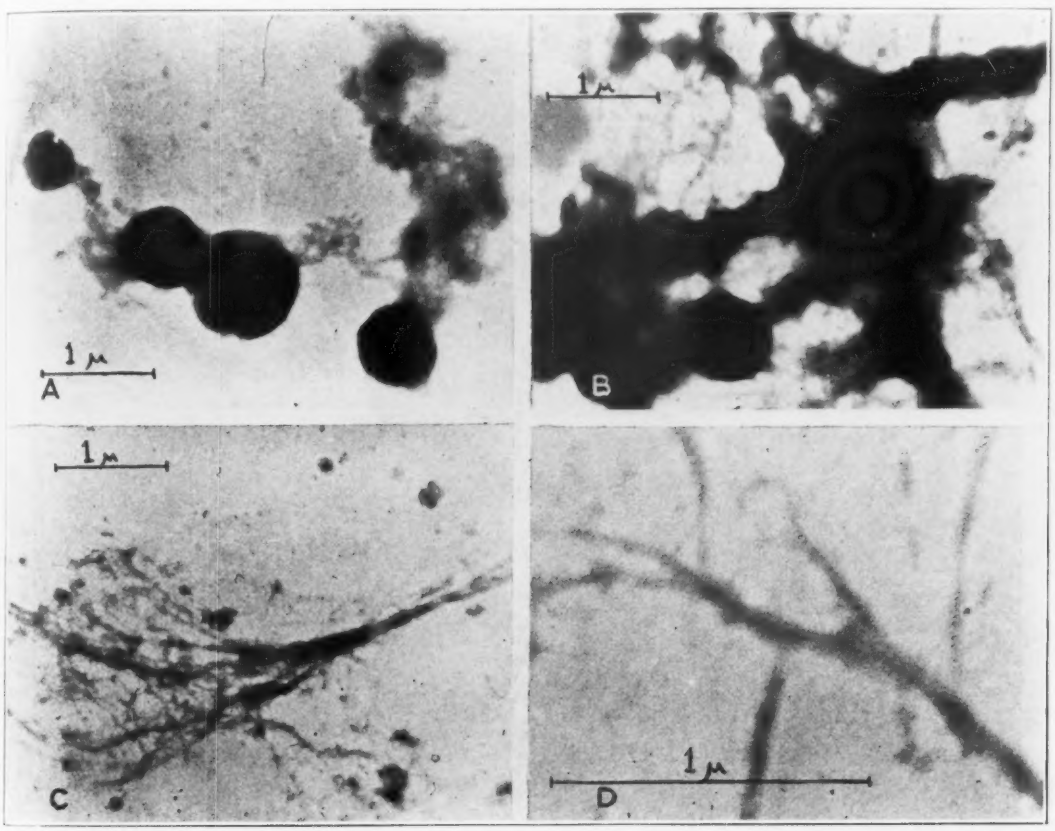

Fig. 5.—*A*, electron micrograph of granules in figure 4 *B* on which is absorbed albuminous material (15,333 diameters); *B*, electron micrograph of granules extracted from rat liver cell carrying albuminous and fibrous material (same magnification); *C*, electron micrograph of sprayed fibrils constituting fibrous materials from the cell; *D*, electron micrograph of fibrils in *C* at magnification of 43,800 diameters.

ELECTRON MICROGRAPHS OF COSMETICS

Returning again to the field of dermatology, a subject of interest to dermatologists is the structure at magnifications of 100,000 diameters of the finest air-spun cosmetic face powder, of which many varieties have been photographed. The individual particles vary greatly in size and shape. Some seem to be thin flakes (fig. 6) piled

6. Clark, G. L.; Quaife, M. L., and Baylor, M. R. B.: Electron Microscope Studies of Proteins Including Some Hemocyanins and Nucleoproteins, Biodynamica **4**:153-162, 1943.

7. Baylor, M. R. B.; Severens, J. M., and Clark, G. L.: Electron Microscope Studies of the Bacteriophage of Salmonella Pullorum, J. Bact. **47**:277-285, 1944.

one on top of another like the leaves of a book; others are rod like with sharp jagged ends or sometimes rounded ends (fig. 7). One familiar brand consists of particles with a fearful array of sharp jagged hooks and spines. Correlations with cutaneous irritation is still lacking, but technic offer in attempts of identification of cellular components.

To answer this question, the bacterium Rhizobium leguminosarum was used as the test specimen for well known stains. The control shows intercellular inhomogeneities, the nature of which

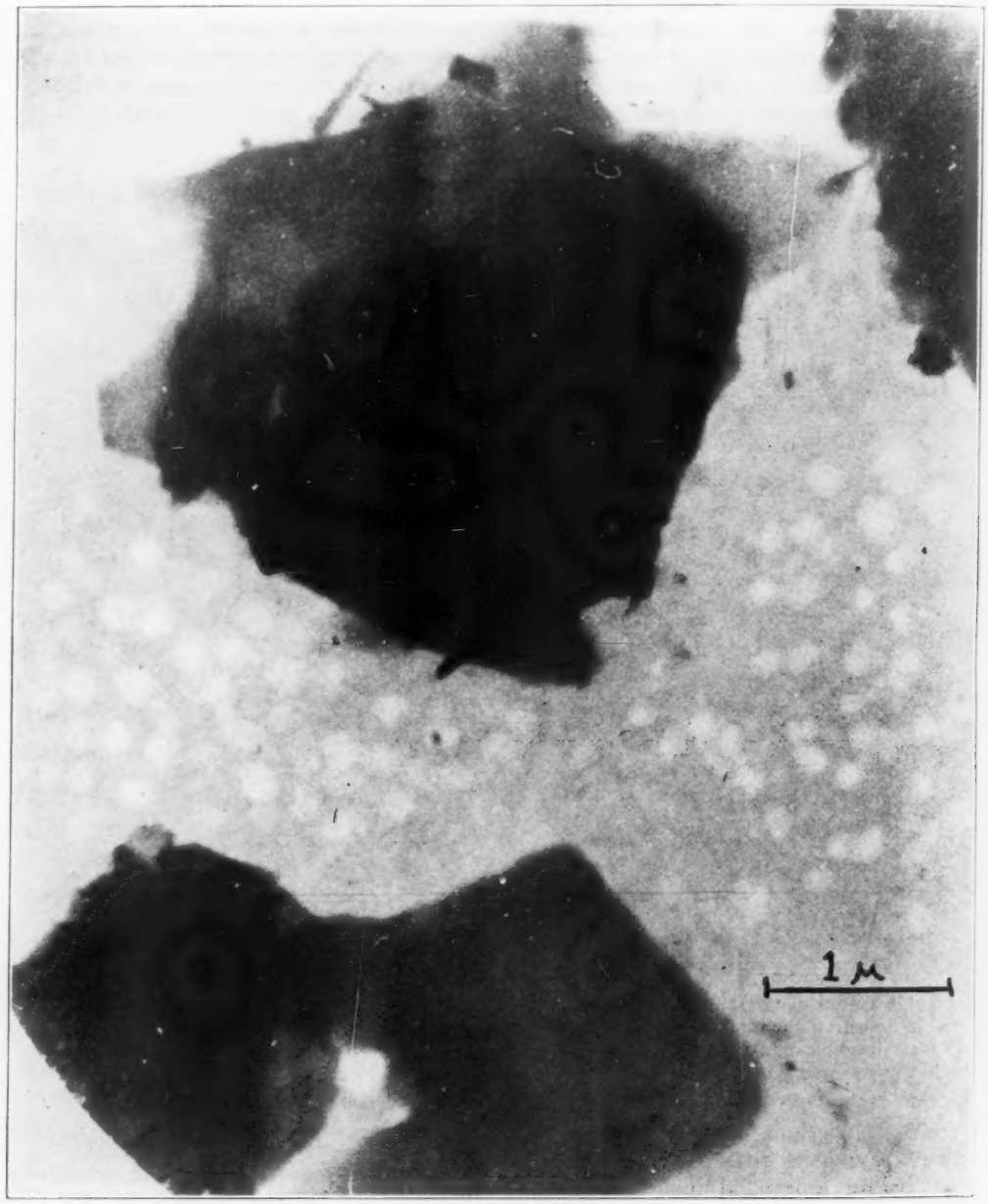

Fig. 6.—Electron micrograph of a widely used face powder at 25,000 diameters.

surely a reexamination of the dermatologic effects of cosmetics is now indicated.

FIXING AND STAINING TECHNICS

Since it would be desirable to study animal tissues under the electron microscope, it has been asked what classic histologic fixing and staining it would be desirable to know. Classic cytologic technics were employed, without hopes of gaining much information but with the idea that if the densities of certain materials could be increased or decreased differentially perhaps some clues might be gained. Since it must be for differences of density that one must look,

fixatives and stains containing heavy metal groups were employed. Also solvents which theoretically would remove differentially certain specific substances were tried.

With mercury bichloride as fixative, the cytoplasmic mass is shrunken and so dense that the electron beam cannot penetrate it. Silver nitrate shows a similar picture. Careful fixation with osmic tetroxide offers greater possibilities. Mayer's hematoxylin as a stain appears to be deposited heavily on the ghost cells, but it does not differentiate any of the internal structure of the living cell. The same condition is found after staining with Heidenhain's hematoxylin.

Cells soaked in solution of sodium bicarbonate for two and one-half hours present an interesting appearance. Mudd had reported that such treatment rendered the cytoplasm extremely transparent. Our micrographs confirm this observation for the granules stand out clearly. Mersky and Pollister expressed the belief that they had extracted the nucleoprotein of vertebrate tissues by soaking in 1 molar solution of sodium chloride. The extracted material shows the same physical properties (absorption bands in the ultraviolet, flow birefringence, etc.) as purified nucleoproteins. Slices of tissue show completely empty nuclei. Bacteria treated in this fashion

Fig. 7.—Electron micrograph of another popular face powder at 25,000 diameters.

clearly show voids in the internal structure. However, treatment with sodium bicarbonate followed by sodium chloride exposed the granules which were hidden by the dense protoplasm. Soaking in sodium bicarbonate solution to clear the protoplasm followed by soaking in an organic solvent likewise does not remove the granules.

Acid treatment which precedes a Feulgen stain and has been claimed by Hiauysi and Mudd to remove nuclear granules has yielded nothing on the organism investigated in our laboratory.

These are but a few of the achievements and possibilities of the electron microscope as a new research and diagnostic instrument in the hands of the dermatologist. Only the barest beginning has been made on the skin itself, and that has been somewhat discouraging. However, there is not the slightest doubt that success will attend further efforts to prepare suitable specimens for examination at a magnification of 100,000 diameters. Unknown facts of the structure of skin will be revealed, and on this basis a great step

Fig. 8.—Electron micrograph of another popular face powder at 25,000 diameters.

The Feulgen stain, which has been used by a German investigator with what he considered to be some success, has also shown nothing with either this organism or the salmonellas.

In general, classic cytologic technics have offered little to electron microscope preparations. The theory of differentially altering densities may still be valid, but much work correlating results of optical and electron microscopy is needed. However, the hopes held out by the new electron analyzer may remove the necessity of such detailed and tedious work.

forward in the science of dermatology can be made. Penicillin has been called the Cinderella of medical science; the electron microscope is the story of Alice in Wonderland.

ABSTRACT OF DISCUSSION

DR. GREGORY SHWARTZMAN, New York: The electron microscope is a marvelous instrument. Dr. Clark's new work is fully appreciated by those who are familiar with the difficulties found in its application to the fields of biology and medicine.

I believe that future progress may be aided by indicating not only the advantages but the limitations of this

new investigative approach. Dr. Clark has already done so. I shall only add some general statements in the light of my personal experience.

It is quite obvious that there exist two significant applications of electron microscopy in medicine: (*a*) observations on hitherto invisible viruses and (*b*) studies at greater magnification and resolution, on bodies already investigated with the light microscope. As physicians our interest is greatest in the first application, in view of medical importance of diseases caused by viruses.

The difficulties experienced with viruses come from the fact that they are obtainable only from infected animal tissues and therefore are necessarily contaminated with cell and tissue debris. Several investigators carried out extensive purifications of the viruses by chemical means, ultracentrifugation, etc., preliminary to examination.

In most of the studies the purified materials yielded round and oval bodies devoid of any morphologic characterization and similar to normal cell constituents, except possibly differing in size. In order to make the images clearer, Beard and his co-workers found it necessary to introduce another complicating factor—the addition of calcium chloride to the preparations.

Thus far, unfortunately, the drastic methods of purification of viruses have been in all probability responsible for the absence of typical morphologic characterization.

I don't want to state that the task of observing viruses with the electron microscope is a hopeless one; I merely wish to point out that new methods for purification and separation from the tissue debris must be worked out. I shall illustrate this point by relating shortly my personal efforts in this direction on the virus of the lymphocytic choriomeningitis. In preliminary studies, it was observed that the virus may be easily adsorbed on glass surfaces. This observation made then possible the purification of the virus without causing great damage to the virus itself. Thus, a section of the infected brain was brought into contact with several hundred capillary tubes; the fluid was removed immediately, and the capillaries were washed with Locke's solution.

Now, these washings were water clear, contained very little nitrogen, were highly infective and showed bodies of characteristic appearance.

Thus it seems that those methods have to be chosen for purification which are likely to cause the least morphologic damage; otherwise, the greatest advantage of the instrument may be lost.

The observations by Dr. Clark clearly demonstrate how valuable the results may be if the methods of preparation are well selected and applied to suitable materials. By the same token, new fields come into view—only to draw your attention to the striking photographs of chromosomes, the fine structure of spermatozoa and his most valuable observations on cosmetics.

The studies on intact cells and tissues, as pointed out by Dr. Clark, are still complicated by the necessity to obtain extremely thin films and by the fact that the high vacuum in which the examination is made may produce coagulation of certain proteins.

In my studies on bacteria and viruses, the films mounted on specimen holders were dried in vacuo from the frozen state and quickly introduced into the microscope. Coagulation was frequently avoided; clearer images were obtained, and not infrequently viable microorganisms could be recovered after exposure to the electron beam. The limitation was, however, in the fact that the low temperature frequently produced some crystallization of cell constituents distorting their appearance.

To sum up, broadly there are two approaches to electron microscopy. Some investigators approach it as physical chemists, with disregard for morphology. Their interest is to determine the diameter of the particles observed. Since better methods exist for determination of size, such as electrophoresis, which represent a large mass of particles, it is obvious that this approach does not bring about the best advantage of the electron microscope. Others, however, approach the field as microscopists with respect for and interest in morphology, and this is the manner in which Dr. Clark approached the subject.

DR. GEORGE L. CLARK, Urbana, Ill.: There has been a great deal of, one might say, ballyhoo about the electron microscope, and much of it has been, I think, unfortunate; but those of us who are working with it are enthusiastic; we believe in it, we believe in its great possibilities and we hope that next year and in the years to come we may have the privilege of reporting again the progress that we are able to make in the field of dermatology.

CHROMOBLASTOMYCOSIS

REPORT OF THE FIRST CASE OBSERVED IN THE CANAL ZONE

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MAJOR WRAY J. TOMLINSON
MEDICAL CORPS, ARMY OF THE UNITED STATES

Although chromoblastomycosis is a comparatively rare disease, it has been reported from widely scattered points on the globe. In 1941 Weidman and Rosenthal [1] summarized this subject thoroughly, including the data on 110 cases reported up to that time. Seven cases were from the continental limits of the United States, but the greatest number were from the Caribbean area (Cuba, Puerto Rica and Costa Rica) and Brazil. Since then additional cases have been reported from Cuba by Pardo-Castello, Leon and Trespalacios [2] and from the Union of South Africa by Simson, Harington and Barnetson.[3] Moore, Cooper and Weiss [4] have recently reported 2 additional cases from the United States. We wish to report the first case recognized in the Canal Zone and cultural studies of the causative fungus.

REPORT OF CASE

D. M., a 74 year old Jamaican, came to the Canal Zone in 1915 and was employed as a carpenter until 1935, when he started farming. He was first seen at Gorgas Hospital on April 12, 1943, because of two verrucous lesions of the left ankle. He stated that this eruption had started about two years previously on the back of the heel and recalled that he had "jabbed" this heel on the thorn of a black palm "several months" before the first lesion appeared. A few months later a similar lesion developed on the outer aspect of the left ankle. Both of these were present when he had an intracranial hemorrhage necessitating admission to the hospital for care. After admission a third lesion appeared on the inner aspect of the left heel. The lesions were tender, especially when touched by his shoe.

The original and largest lesion (fig. 1) was over the achilles tendon of the left heel and measured 2 by 4 cm. The lesion on the outer aspect of the ankle just below the external malleolus was 2 cm. in diameter, and the one on the inner side of the heel was 1 cm. in diameter. The lesions were sharply defined, elevated and verrucous, and were firm and hard to the touch. They were dry, and no ulceration or pyogenic infection was present. When a biopsy was made, the tissue was hard, almost cartilaginous.

On April 13 and again on April 27, 1943 tissue was removed for microscopic examination and culture. On May 20 the 3 lesions were removed by curettement and electrodesiccation. Healing was slow owing to the location of the lesions and the age of the patient. By July 31 the lesions on each side of the heel were healed but there was still a crust on the large lesion over the achilles tendon. When seen Oct. 23, 1943, several small nodules were present along the upper border of this large lesion, and the patient was readmitted to the hospital. The recurrent lesion over the achilles tendon was curetted, and it was found that the entire scar area was undermined. This entire area (1.5 by 3.5 cm.) was thoroughly curetted, and the base was cauterized with the actual cautery. The lesion healed slowly, and on December 11 there was only a thin dry scale present. When seen Jan. 15, 1944 this was entirely healed, and all three lesions are still healed, seven months after the last treatment.

HISTOLOGIC EXAMINATION

There was pronounced epidermal hyperplasia and edema with elongation of the intrapapillary pegs. In these pegs were many small granulomatous abscesses (fig. 2) containing from three to five small dark brown sporelike structures measuring 12 to 15 microns in diameter. The abscesses contained neutrophils, small lymphocytes, plasma cells and some epithelioid giant cells. None of the sporelike bodies were contained in the giant cells. There were scattered areas of abscess formation throughout the papillary layer of the dermis, and many of these contained the sporelike brown bodies.

CULTURAL STUDIES

After the diagnosis was established by histologic examination, macerated fragments of tissue were cultured on Sabouraud dextrose agar and dextrose–yeast extract mediums.[5] Sets of

From the Dermatology Department of the Medical Service and the Board of Health Laboratory, Gorgas Hospital, Ancon, Canal Zone.

1. Weidman, F. D., and Rosenthal, L. H.: Chromoblastomycosis: A New and Important Blastomycosis in North America, Arch. Dermat. & Syph. **43**:62 (Jan.) 1941.

2. Pardo-Castello, V.; Leon, E., and Trespalacios, F.: Chromoblastomycosis in Cuba, Arch. Dermat. & Syph. **45**:19 (Jan.) 1942.

3. Simson, F. W.; Harington, C., and Barnetson, J.: Chromoblastomycosis: A Report of Six Cases, J. Path. & Bact. **55**:191 (April) 1943.

4. Moore, M.; Cooper, Z. K., and Weiss, R. S.: Chromomycosis (Chromoblastomycosis), J. A. M. A. **122**:1237 (Aug. 28) 1943.

5. Kurung, J. M.: The Isolation and Identification of Pathogenic Fungi from Sputum, Am. Rev. Tuberc. **46**:367 (Oct.) 1942.

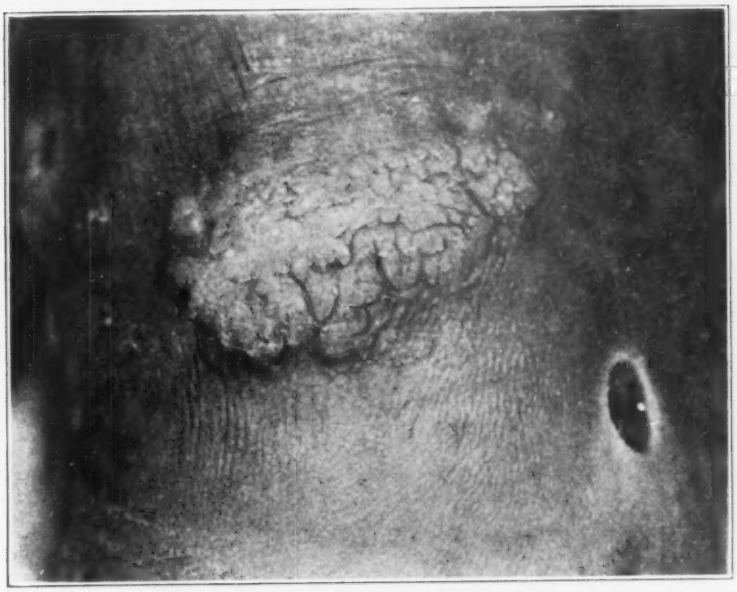


Fig. 1.—Verrucose lesion over achilles tendon of left ankle. × 2.

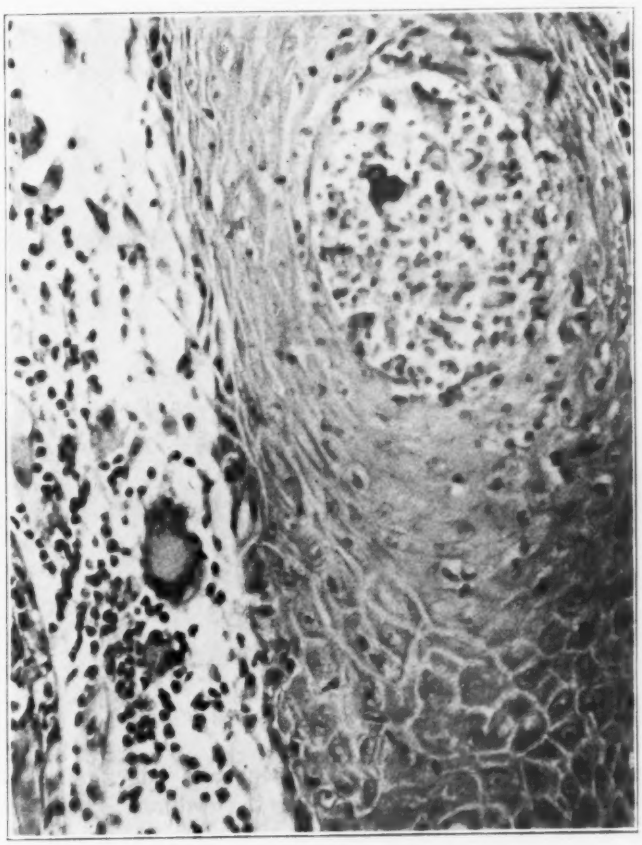


Fig. 2.—Sporelike bodies in intrapapillary abscess. × 540.

cultures were kept at room temperature and others were incubated at 37.5 C.

Results of Cultures.—No growth occurred on the original Sabouraud medium. In seven days an olive green growth appeared on the dextrose-

up to 0.7 cm. in diameter and presented a firm green-brown umbo and a green-black base, with extension of this color into the medium. At two months, the colonies measured up to 2.5 cm. in diameter, were green-black and had irregular

Fig. 3.—Appearance of a two month colony of F. pedrosi var. communis grown on Sabouraud dextrose agar. × 3.

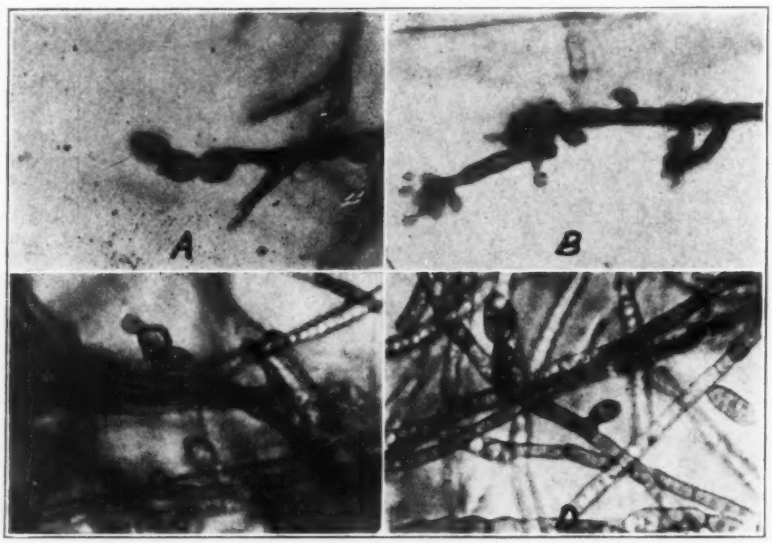


Fig. 4.—Photomicrographs of variations found in F. pedrosi var. communis. *A*, hormondendrum variant, × 750; *B*, acrotheca variant, × 750; *C*, philalophora variant, × 750; *D*, aberrant form, × 750.

yeast medium in the incubator; cultures at room temperature on this medium showed growth three days later. Transfers from the dextrose-yeast medium to the Sabouraud medium grew well.

Gross Appearance of Colonies. — After two weeks the colonies were black-green, measured

crowns and edges (fig. 3) extending slightly into the medium. The hyphae were repent, short and somewhat powdery.

Microscopic Appearance of Fungus.—The hyphae were septate, with occasional racket-like structures. The predominant method of sporula-

was an acrotheca arrangement (fig. 4 *B*), and a few phialophoras were observed (fig. 4 *C*). Extensive search was necessary to demonstrate a few hormondendrum heads (fig. 4 *A*).

Classification of the Fungus.—The fungus recovered resembles Fonsecaea pedrosoi var. communis, showing the integrating forms (fig. 4 *D*), which probably, according to Carrión,[6] represent connecting types between the other three varieties described by him, namely, F. pedrosi var. typicus, F. pedrosi var. cladosporiodes and F. pedrosi var. phialophorica.

6. Carrión, A. L.: Chromoblastomycosis, abstracted, Trop. Dis. Bull. **40**:410 (May) 1943.

SUMMARY

This case of chromoblastomycosis is the first case of the disease reported from the Canal Zone. The fungus recovered was classified as F. pedrosi var. communis. The lesions have remained healed seven months after removal by curettement and cauterization.

NODULAR NONSUPPURATIVE PANNICULITIS (WEBER-CHRISTIAN DISEASE)

PRELIMINARY REPORT OF A CASE CONTROLLED BY SULFAPYRIDINE

HARRY L. ARNOLD JR., M.D.
HONOLULU, TERRITORY OF HAWAII

The most recent reports of relapsing febrile nodular nonsuppurative panniculitis indicate that up to now the disease has not been found to respond to any treatment. Miller and Kritzler,[1] in 1942, reported the first autopsy on a patient dying of this disease; they had given their patient sulfanilamide, sulfathiazole and sulfadiazine successively, with only transient benefit from sulfanilamide. They decided in retrospect that even this benefit was merely apparent and that the sulfonamide compounds were of no value. Sulfapyridine was apparently not tried. Christian's recent edition of Osler's textbook,[2] which shortens the name to "relapsing febrile nonsuppurative panniculitis," contains the statement that "treatment should be symptomatic" and does not refer to any reported successful treatment or mention the use of sulfonamide compounds. Larkin, De Sanctis and Margulis,[3] in February 1944, reviewed the literature and reported the twenty-eighth case of the disease; they mentioned disappointing results from eradication of foci of infection but did not otherwise touch on treatment. Their own patient recovered spontaneously in about six months. I have found no more recent references than these.

The purpose of this report is to present a typical case of this disease in which sulfapyridine effectively controlled all of the signs and symptoms over long periods.

REPORT OF CASE

M. H., a 27 year old Caucasian stenographer, was first seen in March 1943, because of an eruption limited to the anterior part of the left thigh, consisting of moderately tender, slightly raised, hazelnut-sized deep-seated cutaneous nodules (fig. 1). It had been present and slowly spreading for about four months. The entire involved area felt "knobby." Mantoux tests with 0.00002 and 0.005 mg. of purified protein derivative of tuberculin elicited negative reactions at forty-eight hours, and Kolmer-Wassermann and Eagle reactions of the blood serum were negative. A biopsy failed to show significant histologic changes. Sulfadiazine and then sulfathiazole were given, without benefit.

Fig. 1.—"Marbled" and knobby appearance of the left thigh and two lesions above the right knee. Note the peculiar hirsutism in the involved areas.

The patient returned almost two months later, somewhat worse. General physical examination, including fluoroscopic examination of the chest, revealed nothing of note except a pulse rate of 108, a temperature of 99 F. and moderate diffuse abdominal tenderness. Gynecologic examination showed that this might be explained by ovulation on the left. Otologic consultation, including roentgenograms of the sinuses, showed no significant disease; there was a septal perforation, possibly a sequel of a nasal operation performed eighteen years before.

In June a second and more extensive biopsy was performed (figs. 2, 3 and 4). This showed a deep-seated inflammatory process centering around arterioles and

Fig.
Hemato

Read at the Staff Meeting of The Clinic, Honolulu, June 1944.

1. Miller, J. L., and Kritzler, R. A.: Nodular Nonsuppurative Panniculitis, Arch. Dermat. & Syph. **47**:82 (Jan.) 1943.

2. Osler, W.: The Principles and Practice of Medicine, edited by H. A. Christian, ed. 14, New York, D. Appleton-Century Company, Inc., 1942, pp. 472 and 1187.

3. Larkin, V. deP.; DeSanctis, A. G., and Margulis, A. E.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease), Am. J. Dis. Child. **67**:120 (Feb.) 1944.

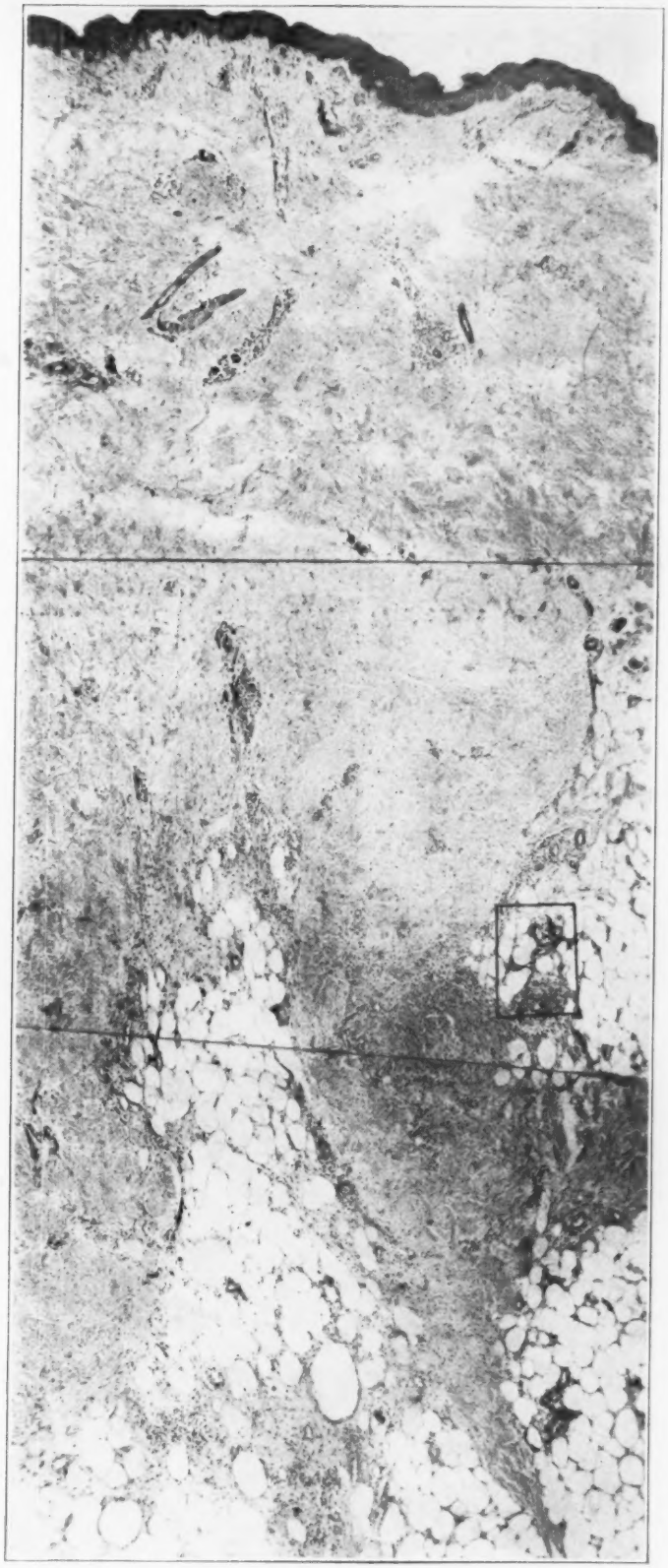


Fig. 2.—Inflammatory infiltrate almost completely limited to the region of the upper part of the fatty panniculus. Hematoxylin and eosin; × 33.

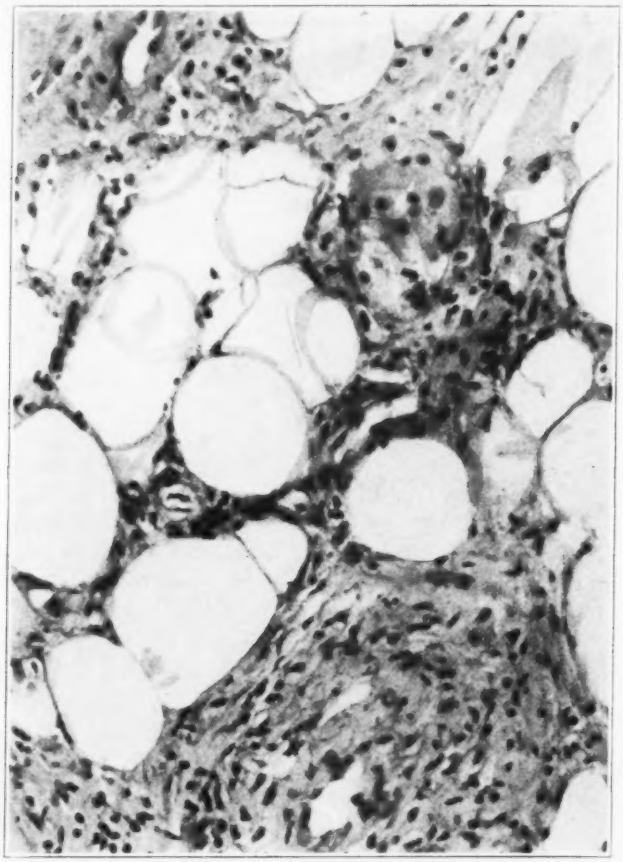


Fig. 3.—Fat-loaded macrophages ("lipophages") and arteriolitis. Hematoxylin and eosin; × 300.

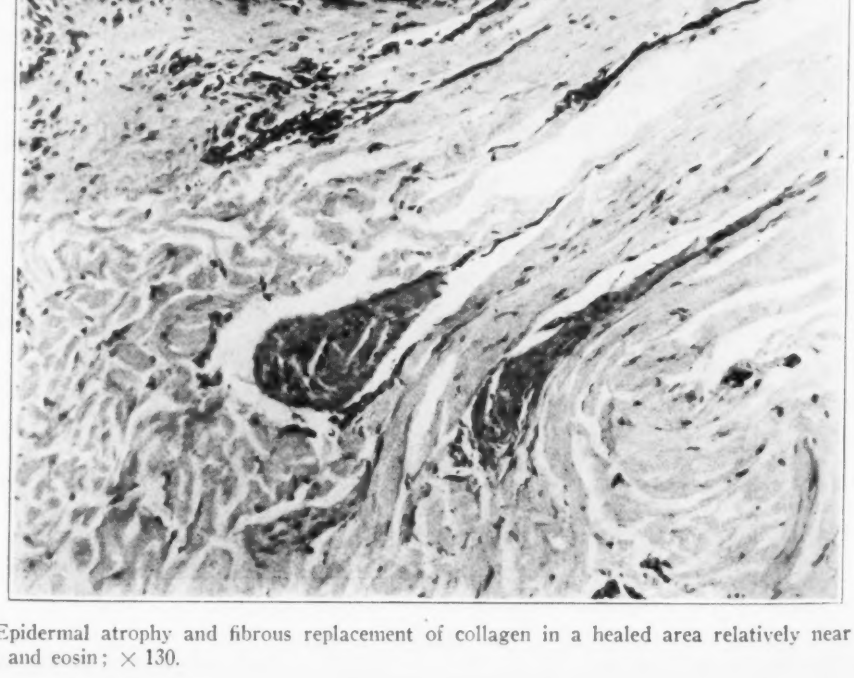


Fig. 4.—Epidermal atrophy and fibrous replacement of collagen in a healed area relatively near the surface. Hematoxylin and eosin; × 130.

arteries and involving the subcutaneous fat. The vessels showed intimal thickening, with occasional obliteration of the lumen and recanalization in places, round cell and polymorphonuclear infiltration and fibrous replacement of portions of the subcutaneous fat; there were several typical macrophages with foamy cytoplasm in the vicinity of the latter process. The relatively high proportion of fibrosis to inflammatory and phagocytic reaction suggested that the lesion selected for biopsy may have been a mature one, already beginning to undergo involution. One section of the epidermis showed atrophy and depression below the surface, strongly suggestive of the depression of healed lesions which is often seen clinically in patients with nonsuppurative panniculitis but which was inconspicuous in this patient.

Two months later the patient returned, reporting that she was much worse; the lesions were slightly more extensive, and though they were still limited largely to the left thigh, isolated nodules had developed on the forearms, chest and opposite thigh. She was feeling too tired to work and was spending much of her time in bed. All the symptoms were aggravated during menses. The white blood cell count was now 12,100, as compared with 10,000 per cubic millimeter in April and May; the differential count was still normal, with slight eosinophilia. The urine contained albumin (1 plus). The cholesterol level of the blood was 180 mg. and serum protein level 7.3 Gm. per hundred cubic centimeters. The Weltmann coagulation band, which had been 5 (minimal shift to the left) on May 24, was now, two months later, down to zero, suggesting extensive and severe exudative disease.

At this point administration of sulfapyridine was begun orally in a dose of 1 Gm. five times a day, with an additional 3 Gm. as the initial dose. Three days later her temperature was normal (it had been over 100 F. daily); the lesions were all bluish, cool to the touch and less tender, and the patient felt decidedly improved, except for slight malaise which seemed attributable to the drug. The sulfapyridine level of the blood was 11.7 mg. per hundred cubic centimeters. Two days later it had risen to 14.7 mg.; the Weltmann reaction was still zero; the sedimentation rate (modified Westergren method: normal 2 to 5 per cent), which had been 15 per cent in May and had risen to 35 per cent on July 30, had dropped to 27 per cent. Clinical improvement was continuing. Two days later, after nausea had interrupted the medication for thirty-six hours, the blood level of the drug had fallen to 9.7 mg. per hundred cubic centimeters; many recent lesions had completely healed, and all the lesions had greatly improved.

Three days later the dose of sulfapyridine was reduced to 0.5 Gm. five times daily because of vomiting; the blood level dropped to 4.9 mg. per hundred cubic centimeters, and clinical improvement became slower and presently stopped. The Weltmann coagulation band had now risen to 5, and the sedimentation rate had dropped to 9 per cent. The dose of sulfapyridine was slightly increased, to 4.5 Gm. a day, with a prompt increase of the blood level to 11 Gm. per hundred cubic centimeters and immediate resumption of clinical improvement.

Late in September a recurrence of an old cardiospasm prevented the ingestion of the drug for a few days, and there was an immediate increase of size, redness and warmth in several lesions, and two new ones appeared on the back. On resumption of the drug these all subsided promptly.

On October 15 use of the drug was purposely stopped, and the patient had a prompt relapse, with recurrence of cutaneous lesions, elevation of temperature, increase of sedimentation rate from 4.5 per cent to 12 and then to 21 per cent and rise of white blood cell count from 5,100 to 9,750 and then to 12,750 over a period of two weeks. The Weltmann reaction, however, remained at 6 (normal) during this period and subsequently. The sulfapyridine level of the blood dropped to zero by the end of the first week. Resumption of the drug was followed as before by prompt remission of symptoms and signs.

On December 6 use of the drug was purposely stopped for the second time; as before, relapse was prompt and within a week virtually complete; also as before, the lesions were neither so extensive nor so severe, and the patient was not so sick as she had been prior to the administration of the drug. Resumption of sulfapyridine again produced prompt remission of all symptoms and signs. Toward the end of January the Weltmann reaction, which had remained at 6 since late in September, rose to 7, while the sedimentation rate fell to 4 per cent.

On February 7 administration of sulfapyridine was again discontinued. This time the relapse was not apparent at all until the fifth day and was not well established till the eighth day; even then it was comparatively mild. On the fourteenth day the cutaneous lesions had nearly all recurred, but tenderness was moderate, limping was slight and the lesions were all smaller than before. The Weltmann reaction had dropped to 5, and the sedimentation rate had risen to only 13 per cent. On the eighteenth day the patient was limping badly and felt ill; the sedimentation rate had risen to 18 per cent and the white blood cell count to almost 12,000, with 72 per cent polymorphonuclear leukocytes and 6 per cent eosinophils. Sulfapyridine was again administered in a dosage of 3.5 Gm. per day in divided doses.

Within two weeks the eruption had again disappeared; the sedimentation rate had dropped to 8 per cent; the Weltmann reaction had risen to 7, and the sulfapyridine level of the blood was 9.1 mg. per hundred cubic centimeters. A month later, on April 11, the Weltmann reaction was still 7 and the sedimentation rate had fallen to 5 per cent—a normal level. The patient felt tired but otherwise well and was working regularly.

On May 19 the sulfapyridine was again discontinued, chiefly because the patient had been taking it continually for nearly three months. Relapse was prompt, occurring within three or four days, but mild; the lesions on June 6 were all well under 1 cm. in diameter; the patient felt well, walked without limping, and was afebrile, and the sedimentation rate was only 23 per cent and the Weltmann coagulation band 5. She felt so well that she preferred, and was permitted, not to resume use of sulfapyridine.

COMMENT

The validity of the primary diagnosis in this case does not seem at all doubtful. The asymmetric distribution is unusual but not particularly remarkable; the absence of well defined depressed scars is probably attributable to the comparative profuseness and small size of the individual nodules; the relatively severe vascular damage in the sections is also unusual but has been reported before in at least 1 case, and, as Weidman [4] implied and as I have felt, the dividing

4. Weidman, F. D., in discussion on Miller.[1]

line between this disease and erythema nodosum is by no means a sharp or clearly defined one. Moreover, the patient has been seen in a relapse by Dr. H. M. Johnson, who originally suggested the diagnosis, and by six dermatologists in the Medical Corps of the Army of the United States,[5] all of whom concurred in the diagnosis.

That the response to the sulfapyridine, whatever its mechanism, has been a specific one, seems almost equally clear. Initially it seemed possible that one was observing the antipyretic effect of the pyridine group rather than the action of the sulfonamide group, but now that five prompt remissions of symptoms and signs on administration of sulfapyridine and five immediate relapses on reduction of the dose or discontinuation of the drug, have been observed over a period of a year (fig. 5), the specificity of action of sulfapyridine seems reasonably well established.

view, and I feel that it is equally applicable to the present case.

Larkin and his associates[3] reported that the literature failed to reveal any laboratory procedures that shed light on the clinical course of the disease. In this case I believe that both the sedimentation rate and the Weltmann reaction shed considerable light on it. The sedimentation rate regularly became elevated when the disease was in uncontrolled relapse, and the elevation was approximately proportional to the severity of the clinical signs and symptoms. The Weltmann coagulation band showed a maximum shift to the left before treatment was started and returned gradually to normal during treatment; during the relapses in December and February it shifted left (to 5) during the relapse, indicating exudative disease, and shifted right (to 7) during the subsequent therapeutic remission,

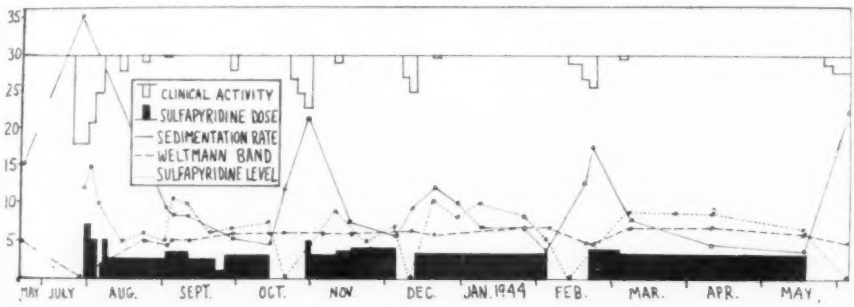


Fig. 5.—Relation of dosage and blood level of sulfapyridine to clinical activity and laboratory observations over a period of a year.

indicating fibrotic disease, presumably fibrosis in the healing lesions. The Weltmann shift was neither sufficiently great nor sufficiently prompt, however, to be of much value in evaluating the patient's status at any given time.

The temptation to regard this action as a specific one on a micro-organism is strong. Only one blood culture was made, and it was negative for pathogens; and no obvious focus of infection was found; yet a response to a sulfonamide drug offers rather strong presumptive evidence that an infection existed. Perhaps the weakest point in such an argument was the failure of the drug to produce remission of symptoms outlasting the period of its administration—in other words, to eradicate the infection, if there was one. However, Walter Lever,[6] in reporting control of a case of acrodermatitis continua (Hallopeau) by continued administration of sulfapyridine, concluded that the therapeutic response favored "the possibility that the disease may be caused by bacterial allergy." I am sympathetic with this

It is interesting to note that dermatitis herpetiformis has generally been found to respond to sulfapyridine more regularly than to any of the other sulfonamide compounds,[7] for it, like Weber-Christian disease, is a chronic relapsing disease which is often aggravated by iodides or bromides or both and which—again like Weber-Christian disease—has been suspected of being caused by bacterial allergy.

SUMMARY

This is the twenty-ninth reported case of relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian disease).

5. Meeting of Civilian and Military Dermatologists Practicing or Serving in Hawaii (unpublished transactions).

6. Lever, W. F.: Acrodermatitis Continua (Hallopeau), Arch. Dermat. & Syph. **49**:273 (April) 1944.

7. Ormsby, O. S.: Avitaminosis in Dermatology and the Value and Limitations of the Sulfa Group in Skin Diseases, J. Michigan M. Soc. **43**:315 (April) 1944.

This case has been observed for over a year, during which time the administration of approximately 3.5 Gm. of sulfapyridine a day has kept the patient completely symptom free and her erythrocyte sedimentation rate within normal limits. On five occasions a relapse immediately followed discontinuance of the medication, and on each of these occasions a remission ensued within twenty-four hours of its resumption.

During clinical activity the erythrocyte sedimentation rate was elevated, and during clinical quiescence it returned to normal levels.

During clinical activity the Weltmann coagulation band was shifted to the left, at one time to zero; during clinical quiescence it was shifted slightly to the right, as high as 7.

CONCLUSIONS

Relapsing febrile nodular nonsuppurative panniculitis may be on the basis of bacterial allergy in some cases.

The erythrocyte sedimentation rate and the Weltmann reaction are of value in evaluating the status of the disease.

Sulfapyridine may be effective in controlling all the outward manifestations of the disease, even when sulfathiazole and sulfadiazine have failed.

Dr. Irvin L. Tilden, of The Clinic, made the photograph and the photomicrographs.

The Clinic, 881 South Hotel Street, Honolulu 53.

CHRONIC DISCOID LUPUS ERYTHEMATOSUS WITH SUPERIMPOSED XANTHOMATOUS INFILTRATION

REPORT OF A CASE

EARL W. NETHERTON, M.D.
CLEVELAND

The occurrence of xanthomatous changes in lesions of a well established dermatosis is exceedingly rare. This process was thought by early investigators to be caused by fatty degeneration or pseudoxanthoma; in recent communications this type of xanthosis is classified with local lipidoses. This phenomenon cannot be differentiated from true xanthoma on the basis of chemical and histopathologic features; however, it differs clinically and probably in pathogenesis.

In classifying diseases of lipid metabolism, Urbach [1] suggested the term "resorption xanthelasma" for this process and stated that it had been known to occur in scars of tertiary syphilids, herpes zoster, laparotomies and acrodermatitis atrophicans. More recently Urbach and Hill [2] supported the assumption that in generalized or essential xanthomatosis there is lipid infiltration, while resorption xanthelasma is an imbibition process. Instead of the lipids' being derived from fatty degeneration of fibrous tissue, cells of diseased tissue absorb cholesterol and related lipids which have become separated from the blood at the site of the disease. They stated that in resorption xanthelasma the blood lipid level is normal.

In 1927 Weidman [3] advocated the use of the term "xanthosis," which was suggested by Siemens, to indicate the yellowing change induced by infiltration of tissue cells by cholesterol and cholesterol esters, particularly when the changes were not manifestations of one of the well established xanthomatoses.

More recently Weidman and Boston [4] discussed at some length the tendency of xanthomatous infiltration to involve granulation tissue or inflammatory processes in which young fibroblasts are present. They observed that this phenomenon may occur in the presence or absence of hypercholesteremia or other manifestations of disturbed lipid metabolism of the whole organism and proposed the term "scar xanthoma" when scars are in any way involved in xanthomatous processes. In contrast to the concept of Urbach and Hill,[2] Weidman and Boston [4] stated the belief that the source of the lipid which induces xanthomatous infiltration in scars is not in itself important.

"Scar xanthoma" seems to be the preferable term. It satisfactorily describes the clinical manifestation of this unusual expression of xanthoma and does not possess the disadvantage of an assumption relevant to its pathogenesis.

Weidman [3] has shown that hypercholesteremia does not make certain the development of xanthomatous infiltration even in lesions containing young, rapidly dividing fibroblasts. He attempted to produce xanthoma by performing biopsies on 10 patients with hypercholesteremia. Five patients had diabetes, 1 of whom also had xanthoma. Another patient had xanthoma tuberosum. In no case did xanthomatous changes develop in the scars of the biopsy, and xanthoma cells were not observed in the specimens.

In animal experimentation Weidman was able to produce xanthosis only once. Dogs infected with pneumococci received large amounts of cholesterol by intraperitoneal injection to determine the value of cholesterol as a protection against pneumococcic infection in dogs. In l

From the Cleveland Clinic.

Read at the Sixty-Fifth Annual Meeting of the American Dermatological Association, Inc., Chicago, June 19, 1944.

1. Urbach, E.: Ueber Lipoidosen mit cutanen Erscheinungen, Klin. Wchnschr. **13**:577 (April 21) 1934; abstracted, Wise, F., and Sulzberger, M. B.: Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1934.

2. Urbach, E., and Hill, W. R.: A Proposed Classification of Cutaneous Lipoidoses, with Description of a New Local Lipoid Dermatosis: Imbibito Lipoidica Collageni Degenerata Cutis, Arch. Dermat. & Syph. **42**:68 (July) 1940.

3. Weidman, F. D.: Studies in Hypercholesterolemia: III. The Approach to the Pathogenesis of Xanthomas, Arch. Dermat. & Syph. **15**:659 (June) 1927.

4. Weidman, F. D., and Boston, L. N.: Generalized Xanthoma Tuberosum with Xanthomatous Changes in Fresh Scar of Intercurrent Zoster: Adenocarcinoma of Ampulla of Vater at Necropsy, Arch. Int. Med. **56**: 793 (May) 1937.

...ng hemorrhagic peritonitis, yellowish red swell-...g on the elbows and severe edema of the scro-...m developed. Superficial crusted ulcers de-...eloped on the edematous scrotum. Frozen sec-...ns of the scrotum and nodules on the elbows ...d not contain true xanthoma cells but did ...ow histologic changes identical with those seen ...the early stages of human xanthoma. Weid-...an considered the experimentally produced ...anthosis to be quite different from the disease ...anthoma. He concluded that xanthoma tubero-...m depends on factors other than hypercholes-...remia and young, rapidly dividing, connective ...sue cells.

They emphasized the need for searching for unknown factors in the pathogenesis of xanthomatous infiltration in scars.

Their patient was a man aged 44, whose illness began as generalized pruritus. Jaundice developed one month later, and during the fifth month of illness cutaneous lesions of xanthoma tuberosum began to develop on the elbows and knees on the rims of the ears and about the mouth. Later, lesions appeared on the palms and on the extensor surfaces of the arms, back and buttocks.

The Wassermann reaction of the blood was positive once but negative later. Old scars on

Case Reports Reviewed by Weidman and Boston

All but 1 of the cases cited by Weidman and Boston have been reviewed and some additional information tabulated. Search for recent cases reported since 1937 has been made. A critical review of the literature on xanthomatosis has not been undertaken here; in recent articles on essential xanthomatosis this rare type of xanthosis is seldom considered.

Author	Sex	Age	Primary Lesion	Associated Xanthomatosis	Hypercholesteremia
...ulich	M	22	Herpes zoster (?); zosteriform arrangement of lesions	Xanthoma tuberosum	Present
...dgway	M	44	Herpes zoster; zosteriform arrangement of lesions	Xanthoma tuberosum	Not stated
...dman and Stokes (Gittings)	F	3	Laparotomy scar and gum following extraction of teeth	Xanthoma tuberosum	Present
...ach	F	54	Nodular ulcerative syphilids	None	Absent
...ser	F	37	Laparotomy scar	Xanthoma tuberosum; xanthoma palpebrarum	Not stated
...ndt	F	..	Postoperative scar	.....	Present; ovarian dysfunction thought to influence lipids
...	F	7	Vaccination scar and site of therapeutic antisyphilitic injection	Xanthoma tuberosum	Present
...ff	M	16	Mosquito bites	Xanthosis diabetica	Present
...rom*	..	11	Herniotomy scar	Xanthomatous papules	.....
...kes and Peck	F	60	Erysipelas	Xanthoma tuberosum; xanthoma of viscera; xanthomatous meningitis	Present
...ven and Knauss	F	9	Festers	Papular and nodular xanthomas	Not stated
...ven and Knauss	F	11	Vesicular eruption	Papular and nodular xanthomas	Not stated

* This reference was not available.

The cause and pathogenesis of xanthoma ...d scar xanthoma are unknown. These entities ...ffer clinically but histopathologically are identi-...l, and in each the cellular metabolism of choles-...rol and related lipids is disturbed. Therefore, ...rtain factors favoring the local deposition of ...olesterol and its subsequent phagocytosis by ...ticuloendothelial cells are probably fundamen-...l and common to both processes.

Numerous reviews of the literature pertain to ...sential xanthomatosis, but few discuss xan-...omatous changes in preexistent dermatoses. ...ven more consideration is given to xanthosis of ...mors, retention cysts and degenerative lesions. In 1937 Weidman and Boston [4] reviewed 12 ...ses of scar xanthoma in the literature and re-...rted an additional case with xanthomatous ...anges in fresh scars of intercurrent zoster. the scalp, arms and shins were considered to be sequelae of late noduloulcerative syphilids.

There was decided hypercholesteremia. Eight months after the onset of illness a zoster developed on the left side of the chest along the distribution of the seventh, eighth and ninth thoracic nerves. One month later xanthomatous papules appeared in the scars of the zoster, and small follicular punctate yellow papules developed just below the lower lip. The uniform spacing of the papules suggested to Weidman and Boston that the xanthomatous changes developed in microscopic scars caused by shaving. Xanthomatous infiltration did not occur in the old syphilitic scars. That xanthomatous changes occur in young scars which contain young, rapidly dividing cells of fibrous tissue rather than in old sclerotic scars was stressed by Weid-

man and his co-workers. This point is demonstrated in all cases in the literature.

Bechet [5] observed a 39 year old woman with a hypercholesteremia, an extensive xanthoma palpebrarum and xanthomatous discoloration throughout a large port wine nevus on the arm. A biopsy was not made; however, the discoloration apparently was caused by diffuse xanthomatous infiltration.

The xanthosis of the nevus in Bechet's case can best be explained on the basis of scar xanthoma occurring in a sclerosing vascular nevus.

Gross and Wolbach [6] recently studied the histopathology of sclerosing vascular nevi. Early in the process the intervascular tissue is very cellular and young fibroblasts are numerous. When phagocytosis of lipid is outstanding in the sclerosing process, the tissues become yellow and are microscopically similar to those seen in xanthoma. The sclerosing process occurs most frequently and the phagocytic properties of the reticular cells are more apparent in the capillary form of hemangioma. Cutaneous hemangiomas are more often involved than those of the viscera.

In 75 per cent of the specimens studied by Gross and Wolbach there was accumulation of lipids or hemosiderin or both in the sclerosed areas. In a few instances these substances seemed to come from hemorrhages within the angioma.

In March 1943 Anderson [7] presented a case before the Los Angeles Dermatological Society, which was similar to, if not identical with, the one reported herein. The case was presented with a provisional diagnosis of xanthoma.

The patient was a woman aged 52, with oval to annular raised erythematous plaques on each side of the neck and the upper portion of the chest. There were also two sharply demarcated, raised, pink to red plaques on each malar region. The lesions extended to the outer canthus of each eye, and their upper margins had a distinct yellowish tinge. Reticulated erythema was present on the lateral surfaces of the arms. A biopsy showed fatty infiltration and xanthomatous changes. Two months later the patient was presented before the same society for the second time.[8] Further investigation revealed that she had nocturnal dyspnea and pain in her chest. An electrocardiogram revealed that she had "heart trouble." The type of heart disease was not stated. The blood cholesterol level was normal.

Anderson was unable to classify his case as an instance of any of the recognized types of xanthomas; however, he stated the belief that the histologic changes were identical with those of xanthoma. In the discussion Goeckerman and Lindsay said that they believed that this was probably a case of lupus erythematosus showing xanthomatous degeneration. Goeckerman stated that he knew of 2 cases in which xanthomatous changes occurred in lesions of lupus erythematosus.

In March 1941 my associate, George H. Curtis, and I presented a patient before the Cleveland Dermatological Society [9] with a provisional diagnosis of xanthoma or of lupus erythematosus with xanthomatous infiltration. After further study I have concluded that it is an example of scar xanthoma occurring in lesions of preexistent chronic discoid lupus erythematosus. As far as I have been able to determine, this is the first case of xanthosis of chronic discoid lupus erythematosus to be reported.

This case adds one more dermatosis to the list of dermatologic entities in which scar xanthoma may occur and is reported in detail.

REPORT OF CASE

A nun, aged 45, came to the Clinic on July 2, 1940. Her chief complaint was an eruption on the face of ten years' duration. She had been told that she had lupus erythematosus and had received various types of treatment, without permanent benefit. Sulfanilamide therapy produced definite improvement but had to be discontinued after a brief period because of the patient's severe hypersensitivity to the drug.

During her youth she had had measles, mumps, varicella and pertussis. She had attacks of pleurisy and tonsillitis. Her tonsils were removed in 1930, and in 1936 a hysterectomy was performed. She seldom had headaches and had no symptoms referable to the cardiovascular system. She was never jaundiced, and her stools were always of normal color. Because of constipation she used compound pills of cascara habitually.

One of her sisters had tuberculosis, and four paternal uncles and one paternal aunt had died of diabetes mellitus.

About 1930 a red area appeared in the right malar region. This lesion gradually enlarged by peripheral extension, and other lesions appeared on the right side of the face. The original lesion finally became confluent with a smaller lesion, to form a large irregular plaque involving the anterior portion of the right side of the face. Recently small light red plaques appeared on the right side of the face and on the lower edge of the right ear.

5. Bechet, P.: Xanthoma Palpebrarum with Xanthomatous Lesions in a Large Congenital Nevus Flammeus, Arch. Dermat. & Syph. **25**:752 (April) 1932.

6. Gross, R. E., and Wolbach, S. B.: Sclerosing Hemangiomas: Their Relationship to Dermatofibroma, Histocytoma, Xanthoma and to Certain Pigmented Lesions of the Skin, Am. J. Path. **19**:533 (July) 1943.

7. Anderson, N. P.: A Case for Diagnosis (Xanthoma?), Arch. Dermat. & Syph. **48**:471 (Oct.) 1943.

8. Anderson, N. P.: Systemic Xanthoma, Arch. Dermat. & Syph. **49**:149 (Feb.) 1944.

9. Netherton, E. W., and Curtis, G. H.: A Case for Diagnosis (Xanthoma? Lupus Erythematosus with Xanthomatous Infiltration?), Arch. Dermat. & Syph. **45**:440 (Feb.) 1942.

In 1937 similar plaques developed in the left malar region and on the left side of the face. Small, poorly demarcated erythematous areas recently appeared on the bridge of the nose. The lesion on the left side of the face also enlarged by peripheral extension, while the lesions on the nose remained the same. Since the onset, the lesions would become edematous and more erythematous when exposed to strong sunshine. This reaction was accompanied by a slight burning sensation.

The time of onset of gradual yellowing of the plaques was not known. Xanthosis of lesions was more pronounced in the left malar region than in the older plaques.

Physical examination revealed hypertension (systolic pressure 170 and diastolic 90) and enlargement of the heart. The liver was smooth and not tender and extended about 3 fingerbreadths below the costal margin.

The eruption was strikingly symmetric, was limited to the face and right ear and had the butterfly distribution commonly seen in chronic discoid lupus erythematosus. The lesions consisted of fairly well demarcated, oval, rounded and irregularly shaped, large and small plaques located in each malar region and on the sides of the face, bridge of the nose and lower edge of the right ear. The eyelids were not involved. In the malar region was a narrow peninsula-like projection of the margins of the plaques, which terminated near the outer canthus of each eye. The lesions varied from pink to light red to a distinct yellow. The smaller and younger lesions were pink or light red, while the larger plaques in the upper and central portion were yellow and the lower margins were erythematous. The central portion of the lesions in the malar regions was depressed and appeared to consist of xanthotic scar. The xanthosis of the eruption in the left malar region was patchy, thereby producing erythematous to yellow reticulation. Yellow discoloration was not so apparent in the smaller and younger lesions. The lesions on the bridge of the nose were small and not so sharply demarcated as those on the face. There was a small dry adherent scale on the lesion on the right ear. Other lesions were not scaly. In some areas the orifices of pilosebaceous follicles were dilated. A few small keratotic plugs were present in follicles of the plaque in the left malar region. It should be noted that follicular keratotic plugs were present in the lesion of three years' duration rather than in the older lesion, which had been present for ten years. Xanthosis was most pronounced in older plaques.

There was an oval depression, caused by tightly fitting spectacles, on each side of the base of the nose. The imprints showed none of the changes characteristic of the lesions on the face (fig. 1).

A roentgenogram of the chest was normal. The urine was normal. The hemogram showed 4,520,000 red blood cells per cubic millimeter, 5,250 white blood cells and a hemoglobin content of 84 per cent. The differential count showed 53 per cent neutrophils, 7 per cent eosinophils, 38 per cent lymphocytes and 2 per cent monocytes. The Wassermann and Kahn reactions of the blood were negative. The blood sugar content three and three-fourths hours after eating was 106 mg. per hundred cubic centimeters. On July 3, 1940 the fasting blood plasma cholesterol level was 200 mg. per hundred cubic centimeters, and on March 27, 1941 four and one-fourth hours after eating it was 187 mg. A Mantoux test with tuberculin (purified protein derivative) in the first strength elicited a negative reaction and in the second strength a positive reaction.

On July 3, 1940 a biopsy specimen of the most xanthotic area was removed from the upper outer portion of the original plaque in the right malar region. In June 1941 a second specimen was removed from the younger lesion on the left cheek to study the earlier histopathologic changes.

Fig. 1.—Symmetry and distribution of lesions frequently seen in discoid lupus erythematosus. Oval depressed areas on each side of the base of the nose were caused by eyeglasses and were not identified with the eruption.

Tissue from the older lesion showed a uniform atrophy of the epidermis. There was a thin layer of hyperkeratosis; the granular layer was thin but intact, and the rete mucosa consisted of four to six layers of prickle cells. The basal layer was intact throughout all sections. Interpapillary pegs had been obliterated completely by changes in the corium. Only a few orifices of the pilosebaceous follicles were dilated, and these contained hyperkeratotic plugs. Except for one follicle the dilatations were not deep, and acanthosis adjacent to the dilated follicle, which is usually seen in discoid lupus erythematosus, was absent.

In practically all of the corium the normal connective tissue was replaced by cellular infiltrate consisting of lymphocytes, fibroblasts, epithelioid cells and large and small foam, or xanthoma, cells. Touton and endothelial giant cells were not observed. In some areas the interstitial stroma was delicate, while in others the stroma was more dense and fibrous and contained more mature fibroblasts and less cellular infiltrate. A few small foci of lymphocytic infiltration were present in the midportion of the corium and about the dilated pilosebaceous follicles. There were only a few atrophic sebaceous glands. The sweat glands were normal.

The foam cells varied considerably in size and were most numerous in the upper and central portion of the corium. Some dilated capillaries were surrounded by small foam cells.

Throughout the corium the small blood vessels were dilated. There was a hyperplasia of endothelial cells in the walls of many dilated capillaries. Small groups of endothelial cells could be traced to the walls of the vessels. A few areas of cellular infiltrate were observed in the upper portion of the subcutaneous fat.

Verhoeff's stains showed complete absence of elastic tissue in the xanthomatous infiltrate. In areas adjacent to the xanthomatous process there was some fragmentation of elastic tissue.

Tissue changes in the left malar region were essentially the same. Unfortunately, frozen sections used for fat stains showed more follicular and perifollicular changes than those used for hematoxylin and eosin stains; consequently these features could not be studied to the best advantage.

Sections stained with sudan III and scarlet red showed a spotty intracellular and extracellular deposit of lipids scattered throughout the upper and middle portions of the corium. The uniform lipid infiltration usually seen in xanthoma was not present. Lipids were not deposited in the cellular infiltrate which surrounded the dilated pilosebaceous follicles.

Polariscopic examination of stained frozen sections showed that the stained lipid infiltrate was doubly refractile. Where the deposit was less dense, double refractile crystals were observed. Therefore the lipid infiltrate contained cholesterol and cholesterol esters.

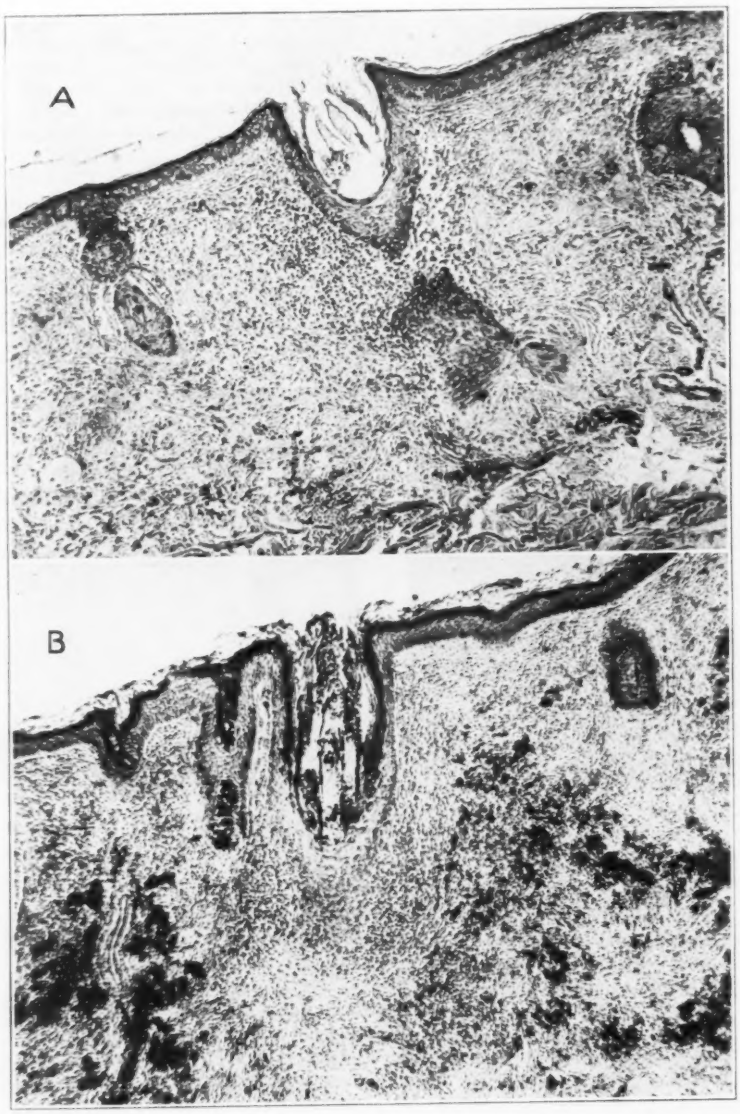


Fig. 2.—*A*, section from the oldest lesion, in the right malar region, showing uniform atrophy of the epidermis and superficial dilated pilosebaceous follicle containing keratotic plugs and moderate perifollicular cellular infiltrate, as well as xanthoma cells in the lower left area (× 75). *B*, frozen section of tissue from younger lesion on left cheek showing changes similar to those in *A* and, in addition, patchy double refractile lipid deposit. Sudan III; × 75.

and confirmed the opinion that the process in this case was one of xanthosis.

To classify further the type of xanthosis, photographs, sections of tissue from the original lesion and an abstract of the history were sent to Dr. Fred D. Weidman. Portions of his informal report are as follows:

"From the histologic standpoint, there is only one feature that supports the diagnosis of lupus erythematosus, namely, the dilatation of the orifices of the hair follicles. This does not occur consistently, is never of high grade and does not extend at all deeply into the pilosebaceous follicle. The epiderm is atrophic in all its parts, whereas in lupus erythematosus one should expect to find some places where it was acanthotic, corresponding to some part of the lesion in which the changes were progressive. I cannot conceive that the epidermal atrophy that occurs in lupus erythematosus would occur in such a uniform fashion throughout a large section like this. It is true that a few foci of lymphocytes can be discovered in the corium, but, again, they do not occur at all consistently throughout the section and are no more than might be expected in connection with the xanthomatous changes.

"As to the xanthomatous changes, they occur in a spotty way that suggests that they are occurring secondarily in some preexistent lesion. The presence of intervening regions of degeneration suggests that the xanthomatous changes are regressing.

"Under all those circumstances, though, I feel that the clinical features should overbalance the shortcomings of the histologic ones and that the case should be regarded as an instance of lupus erythematosus primarily. According to that, one has one more observation of xanthomatous changes superimposed on a well established dermatologic entity.

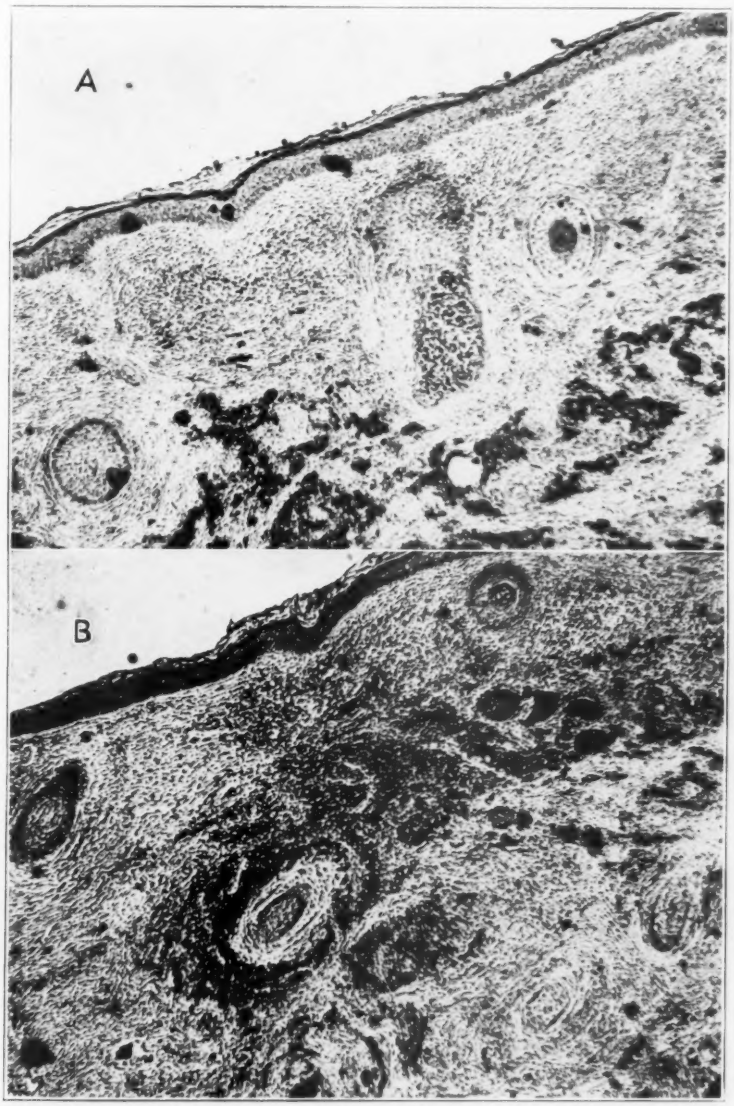


Fig. 3.—Frozen sections from lesion in left malar region showing patchy intracellular and extracellular deposits of double refractile lipids. Note absence of lipid deposit in perifollicular infiltrate and in the more sclerosed areas. Sudan III; × 75.

"I could not speak thus positively were not the photographs so excellent; with the pocket lens I could make out the follicular keratoses, in which connection it appears that the biopsy specimen, the scar of which can be plainly seen, did not pass through a region where the features of lupus erythematosus were more pronounced. This is one of the shortcomings of histologic studies, namely, that the pathologist is confined to study of a limited portion instead of the whole lesion."

xanthomas, to what group of the recognized xanthomatoses do they belong?

The symmetry and the butterfly distribution of the eruption are characteristic of discoid lupus erythematosus and not of any cutaneous xanthoma. The prolonged and relatively persistent erythema with slowly developing patchy xan-

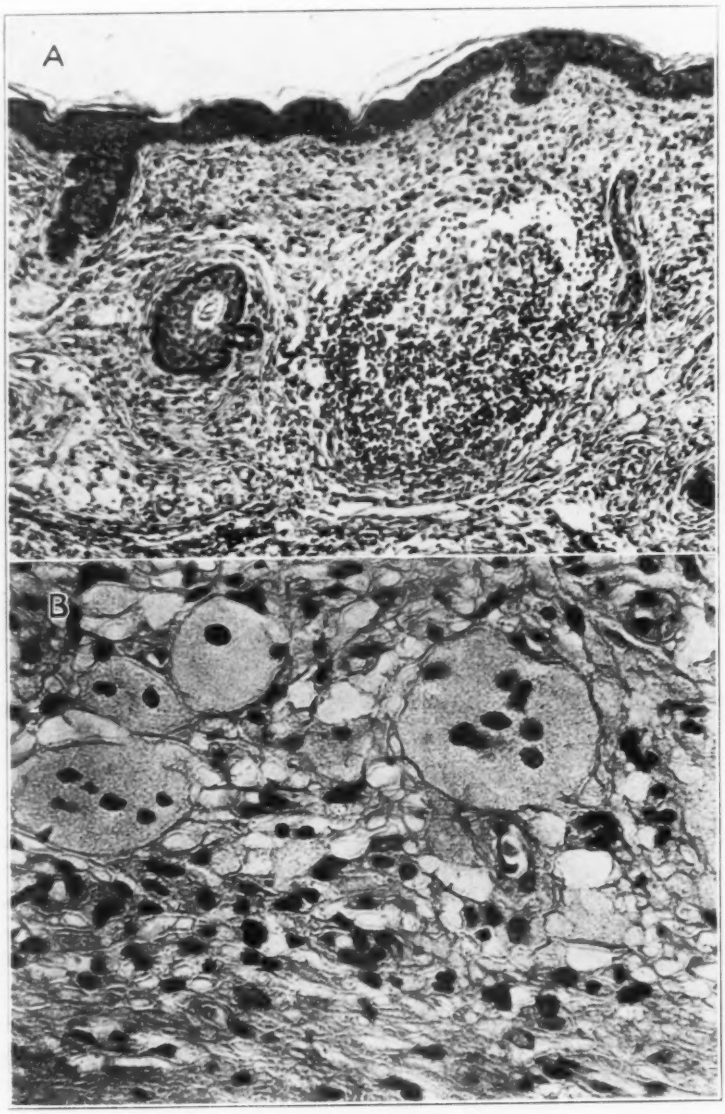


Fig. 4.—*A*, focus of lymphocytic infiltration in corium (× 100). *B*, foam cells seen throughout xanthomatous infiltrate (oil immersion).

COMMENT

This rare case is of special interest from the viewpoint of differential diagnosis and proper classification. Are the lesions primarily cutaneous xanthomas, or are they manifestations of a well established dermatosis with superimposed xanthomatous changes? If they are primarily

thomatous discoloration is not characteristic of xanthoma. Furthermore, the central scarring and dilatation of orifices of pilosebaceous follicles as well as follicular plugging strongly support the diagnosis of lupus erythematosus. The photosensitivity exhibited by the lesions is not uncommon in cases of lupus erythematosus and is not a characteristic of cutaneous xanthoma.

That this may be an unusual xanthoma planum similar to xanthoma palpebrarum is hardly tenable. Xanthelasma starts as flat yellow lesions, and the larger, more familiar xanthoma planum seen occasionally in xanthoma tuberosum does not possess the distinct patch type of xanthosis and follicular changes observed in this case.

Evidence from the clinical course and gross characteristics of the eruption favors a diagnosis of chronic discoid lupus erythematosus in which the xanthosis is a secondary process.

Histopathologic changes tend to support the clinical diagnosis but are not entirely confirmatory. The area from which the biopsy specimen was taken accounts for the variance between clinical and histopathologic observations. Even though follicular and perifollicular changes are not so great as those of uncomplicated lupus erythematosus, they cannot be ignored and are significant when correlated with the clinical features. The lipid infiltration is spotty or less diffuse than that of primary xanthoma. As pointed out by Dr. Weidman in his comment, this feature suggests that the xanthomatous changes were not of a primary nature.

For many years it has been thought that hepatic disease, particularly biliary cirrhosis, is in some way related to the pathogenesis of xanthoma. This point is emphasized in a number of the excellent communications of Weidman and his co-workers [10] and many others. Montgomery and Osterberg,[11] in a comprehensive correlation of the clinical, histopathologic and chemical studies of a large number of various types of cutaneous xanthoma, observed a high incidence of serious cardiovascular disease.

In the present case there was moderate essential hypertension and enlargement of the liver. The patient had never been jaundiced or had symptoms referable to her cardiac or hepatic disease. Unfortunately, I never had the opportunity of investigating this phase of her illness. In view of the present concept of xanthomatosis, hypertension and hepatic disease may have contributed to the pathogenesis of the scar xanthoma in this case. It should be recalled that the patient observed by Anderson had a serious cardiac disease.

An analysis of cases of scar xanthoma reviewed by Weidman and Boston [4] showed that in the majority of instances scar xanthoma occurred in patients who had cutaneous xanthoma of the generalized type or hypocholesteremia or both and that involved scars were young and those of common dermatologic entities. This suggests that scar xanthoma is more likely to occur in patients with generalized xanthomatosis and also that rarity of scar xanthoma in lesions of discoid lupus erythematosus may be due in part to the age of the scar and the infrequent coincidental occurrence of essential xanthomatosis and lupus erythematosus. In a series of 33 cases of lupus erythematosus, Jlinsky [12] found the average blood cholesterol level to be slightly above normal.

On the other hand, the experiments of Weidman [3] and clinical observations show that hypercholesteremia or the presence of essential xanthomatosis does not guarantee the development of xanthomatous changes in intercurrent scars caused by trauma or inflammatory disease. These observations emphasize the complexity of the pathogenesis of xanthomatous processes. For many years a similar confusion existed with regard to the significance of the presence or absence of hypercholesteremia in xanthoma tuberosum. Clarification of this point was achieved by clinical differentiation of xanthoma tuberosum from xanthoma disseminatum; however, nothing was added to the understanding of the causation or pathogenesis of xanthomatosis.

Thannhauser and Magendantz [13] have given a comprehensive summary of the present knowledge of the metabolism and function of cholesterol and have pointed out four possible disturbances in its intermediate metabolism which have been considered in the causation of essential xanthomatosis. There may be a diminished disintegration of cholesterol in the intermediate metabolism, a diminished excretion of cholesterol, a disturbed equilibrium between cholesterol and cholesterol esters or an increased synthesis of cholesterol. After considering these possible general disturbances of general cholesterol metabolism they concluded that there is no evidence to support the assumption that essential xanthomatosis is caused by a disturbance of intermediate cholesterol metabolism. They expressed the belief that the metabolic disturbance of cholesterol is localized in the xanthoma cells, which, according to Waldeyer and others, are embryonal cells which are able to form different

10. Weidman, F. D., and others: Xanthoma and Other Dyslipoides, Chicago, American Medical Association, 1941.

11. Montgomery, H., and Osterberg, A. E.: Xanthomatosis: Correlation of Clinical, Histopathologic and Chemical Studies of Cutaneous Xanthoma, Arch. Dermat. & Syph. **37**:373 (March) 1938.

12. Jlinsky, B. W.: Ueber die Cholesterinämie bei Lupus erythematodes, Dermat. Wchnschr. **96**:739 (June 3) 1933; abstracted, Arch. Dermat. & Syph. **28**:719 (Nov.) 1933.

13. Thannhauser, S. J., and Magendantz, H.: Different Clinical Groups of Xanthomatous Diseases: Clinical Physiological Study of Twenty-Two Cases, Ann. Int. Med. **11**:1662 (March) 1938.

fats and to release the fats by degeneration. They concluded that essential xanthomatosis is a cellular metabolic disturbance caused by an embryonal metaplasia of certain cell groups and prefer to consider it a metaplastic reticular cholesterosis. They expressed the belief, however, that xanthoma cell formation may occur independently of essential xanthomatosis, thereby offering an explanation for the pathogenesis of localized xanthomatous change in certain tumors, cysts and scars.

The solution of the pathogenesis of lipidoses has been retarded chiefly because of the lack of comprehensive knowledge of the physiologic chemistry of general and cellular lipid metabolism.

SUMMARY AND CONCLUSIONS

A case of xanthomatous infiltration occurring in lesions of chronic lupus erythematosus was encountered. The diagnosis of discoid lupus erythematosus as the primary dermatosis is based chiefly on the clinical characteristics of the eruption; however, histopathologic changes were not entirely inconsistent with those observed in lupus erythematosus.

The xanthosis occurred in the scar of a preexistent dermatologic entity; therefore it belongs to the scar xanthoma group of Weidman and Boston or resorption xanthelasma of Urbach.

"Scar xanthoma" is the preferable term. It satisfactorily describes the clinical manifestations of this unusual expression of xanthoma without an assumption relevant to its pathogenesis.

Factors responsible for the deposit of cholesterol and its esters in diseased tissue and the production of cellular changes appropriate for the development of xanthomatous infiltration are unknown. Suffice it to say that scar xanthoma does not involve old scars but, instead, occurs in tissue containing young, rapidly dividing reticular cells, some of which have undergone changes permitting abnormal cellular metabolism of cholesterol and related lipids.

ABSTRACT OF DISCUSSION

DR. FRED D. WEIDMAN, Philadelphia: I shall not have anything to say about the clinical diagnosis—that is, as to whether this case qualifies unequivocally as a case of lupus erythematosus. Assuming that this is correct, I shall discuss only the pathology.

First, what is the possible source of the lipids in cases in which there is no hypercholesteremia? In connection with a xanthosarcoma of the arm, I indicated (Weidman, F. D.: Xanthoma of the Cheek Succeeding Xanthosarcoma of the Forearm, *Arch. Surg.* **34**:792 [May] 1937) that stagnant, decomposing blood in situ might possibly be the source, blood being rich in cholesterol, both in the serum and in the red blood cells. I listed a number of highly vascular lesions which could become xanthomatous, such as hemangiomas. Dr. Netherton's citation of Dr. Bechet's case is another which adds weight to the thesis that blood which is in a state of stasis may predispose to local deposit of lipid. Too, in a case of what my colleague and I chose to call xanthoma pseudodiabeticorum (Weidman, F. D., and Schaffer, H. W.: Xanthoma of the Skin and Larynx, ARCH. DERMAT. & SYPH. **35**:767 [May] 1937, and Weidman, F. D.: Position of "Pseudodiabetic Xanthoma" Among the Lipoid Disturbance of the Skin (Urbach), *ibid.* **35**:815 [May] 1937), there was lipid deposit in a larynx which contained evidence histologically of old hemorrhages. Accordingly, it may be that in this case of Dr. Netherton's, it is the long-standing hyperemia which is a part of lupus erythematosus, with relative stasis, that determined the eventual deposition of the lipoid substances.

A most significant lesson is to be learned from scar xanthomas with respect to classification. As I see it, the logical approach to this is through the clinical channels that Dr. Netherton indicated in the lantern slides. In them, he showed a lengthy list of definitely established, well known clinical conditions; only after that did he consider the matter of classification on the basis of the chemistry, which, while highly important to the chemist, took second place.

To cite another example which bears on principles of classification: When we were discussing Dr. Ketron's paper on erythema elevatum diutinum this morning, an alternative diagnosis of extracellular cholesterosis was advanced. It would be interesting to learn whether a reexamination of all the cases of extracellular cholesterosis would demonstrate that in them there is the histologic structure of erythema elevatum diutinum plus cholesterol. In other words, is extracellular cholesterosis simply erythema elevatum diutinum with the more or less fortuitous addition of a lipid phase? If so, I should be opposed to the acceptance of extracellular cholesterosis as a clinical entity. It should be "cholesterotic erythema elevatum diutinum" or "erythema elevatum diutinum with superimposed extracellular cholesterosis." This is in line with a contention that I have long held, namely, that in developing the classification of the lipoidoses, one should not add more and more of them as entities simply because they exhibit this or that particular fatty feature. For example, Urbach's "imbibitio lipoidica collageni degenerati cutis" (Urbach, E.: A Proposed Classification of Cutaneous Lipoidoses, ARCH. DERMAT. & SYPH. **42**:68 [July] 1940) is nothing more nor less than a dermatofibroma in which an excessive deposit of fatty substance has taken place; it is synonymous with the conventional dermatofibroma lenticulare. Incidentally, the hemosiderin deposits seen in that disease are doubtless an indication of previous hemorrhage, and the hemorrhage, in turn, may be the source of the locally deposited fats in that condition. Urbach's "imbibitio lipoidica telae elasticae degeneratae" is open to the same order of criticism. It appears to be synonymous with senile elastosis or sailor's skin. By no means should one interminably build up a complicated structure of new clinical lipid entities supplied from previously existing, well known, clinical dermatologic entities to which merely fat has been added.

To conclude with a final note concerning scar xanthomas, actual scars need not be seen in order to satisfy the criteria. Thus, the reactive pathologic processes need not proceed as far as fibrous tissue hyperplasia. Following erysipelas and eczema, lipoidal substances may be added to the pathologic picture and give rise to xanthomatous appearances.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I might add 1 other case to those of Dr. Netherton, namely that of a patient which I reported (Montgomery, H.: Xanthomatosis: Cutaneous Xanthoma, Especially in Relation to Disease of the Liver, *J. Invest. Dermat.* 1:325-351 [Oct.] 1938) as a probable instance of Bürger-Grütz disease or of hepatosplenomegaly with cutaneous and mucous membrane lipidosis. This patient had xanthelasma of the eyelids, xanthoma tuberosum on the elbows, xanthomatous deposits in the mucocutaneous surfaces of the mouth and hyperlipemia, especially an increase in phosphatides, but, in addition, had xanthomatous deposits in the laparotomy scar, the patient having had several operations.

The possibility arises in Dr. Netherton's case, in which there was enlargement of the liver even though there possibly was no hyperlipemia, that there may have been a generalized disturbance in cholesterol metabolism. It is known that xanthomatous lesions can occur secondary to hepatic disease. In xanthoma disseminatum or disseminate types of xanthomatosis in which there is no hypercholesteremia or hyperlipemia, there still may be hepatic involvement. A disturbance in lipid metabolism might explain, therefore, the xanthomatous deposits in an area of lupus erythematosus, the selection of this site resulting from a lowering of the normal resistance of the skin by the lupus erythematosus.

DR. NELSON PAUL ANDERSON, Los Angeles: The question arises as to whether this is really a case of primary lupus erythematosus with secondary xanthomatous changes, as suggested by Dr. Netherton, or whether the disease is primarily a xanthoma with changes which superficially resemble lupus erythematosus.

If Dr. Netherton's idea is correct, namely, that this is primarily lupus erythematosus with secondary xanthomatous changes, the question arises, why it is not encountered more frequently. After all, lupus erythematosus is not a particularly rare disease. As suggested by Dr. Netherton and Dr. Montgomery, the idea has occurred that perhaps cases such as the present one are instances of lupus erythematosus occurring in persons with hepatic disease and that that particular group of patients tend to have secondary xanthomatous changes take place in their lesions of lupus erythematosus.

I can add *2* cases to the group that has been mentioned: 1 that has already been reported and 1 that was observed last February. The clinical features appear to be striking. The lesions are symmetric and occur particularly in the malar regions. At first glance and at a distance they appear to be lupus erythematosus. When one examines them closely, one sees a peculiar, yellowish tinge to them. But after hearing Dr. Netherton's excellent presentation I feel that he has reached the right conclusion, namely, that the disease is primarily lupus erythematosus with secondary xanthomatous changes.

DR. EARL W. NETHERTON, Cleveland: I am glad to have Dr. Weidman emphasize, as he has done so very well in his writings, that this disease is xanthomatous involvement of scar tissue containing young fibroblasts. This process is best designated by the term "scar xanthoma" rather than by that suggested by Urbach.

As to the source of the lipids from hemorrhage or stagnant blood, Gross and Wolbach, as cited in the paper, in studying sclerosing hemangiomas pointed out that in some of their specimens they believed that the source of the lipid was interstitial hemorrhage. They observed phagocytosis of lipids and hemosiderin in their sections. The sclerosis was greatest in the capillary type of angioma, involving the skin, rather than in the vascular type, involving viscera. It may be that stagnant blood or interstitial hemorrhage is a source of the lipids in some cases of scar xanthoma.

ALOPECIA CIRCUMSCRIPTA DUE TO VITAMIN A DEFICIENCY

REPORT OF A CASE

S. GILL, M.D.

HAIFA, PALESTINE

A 40 year old woman of an Arab village was sent to me by the local physician for treatment of tinea capitis, a disease frequent in Palestine.

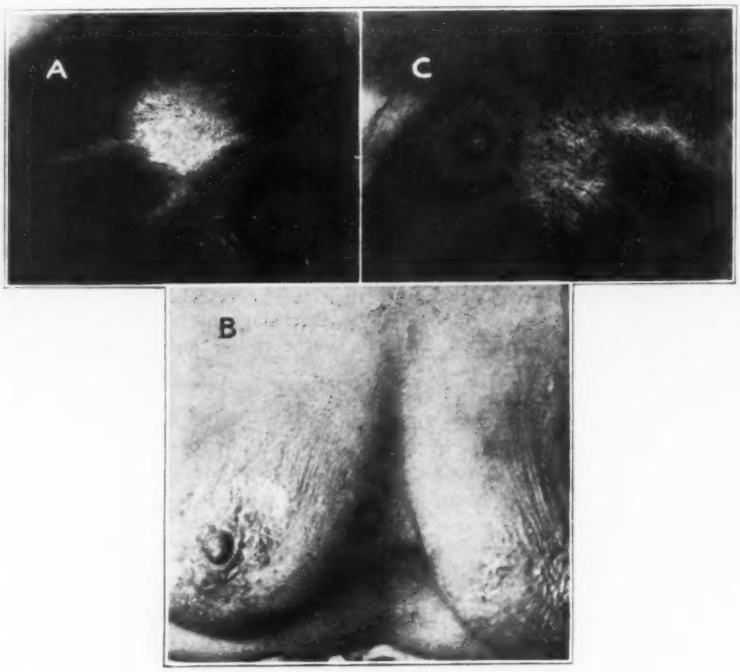
Examining her scalp, I saw an isolated plaque with incomplete alopecia, 3 by 4 cm. in extent, with irregular, ill defined limits. The area was covered with a mass of coarse adherent scales, elevated above the surface. There were no signs of inflammation. Hairs of various lengths protruded above the white mass. They had not lost their pigmentation. The shortest of them showed resistance to the epilating forceps while they were being removed for examination.

Microscopic examination of the hairs and scales after they had been soaked in 30 per cent solution of potassium hydroxide did not reveal mycelium or spores. A repeated microscopic examination after local applications of 5 per cent solution of dextrose during twenty-four hours showed the same picture.

The skin of the face was dry. The nose and the adjacent parts of the cheeks, the chin and the upper lip in some places were scaly, rough and harsh and partly depigmentated and partly of a dirty slate color. The hyperkeratotic papules on the face were rather flat and contained no visible spines.

The skin of the body was xerodermatic and rough, with symmetrically distributed areas covered with spinous papules. The mammary region, discolored to some degree, was covered with follicular and perifollicular hyperkeratotic masses.

Moderate itching had led to numerous excoriations. The palms and soles remained unchanged. The nails showed longitudinal ridges. The conjunctivas were unaffected, and there were no complaints of visual disturbances or night blindness. According to the patient's statement, the changes on her skin had begun only some months previously. At the time of examination her complaints were increasing weakness and fatigue, abdominal pain and lack of appetite. Her diet showed a lack of nutritive essentials, as it consisted mostly of rice, legumes, mutton fat, bread and black coffee. She seldom ate vegetables and fruits and had a meat dish only about once a month, while milk, eggs and butter were rarities to her. Considering the typical cutaneous lesions and the deficient and faulty nourishment of the patient, it was not difficult to conclude that the dermatosis was due to vitamin A deficiency, though I had no opportunity to confirm it either through measurement of dark adaptation or through estimation of the vitamin A level of the blood.



A, circumscribed patch of alopecia; *B*, follicular hyperkeratoses; *C*, return of hair after treatment with vitamin A.

I prescribed a daily ration of 4 glasses of milk, 3 eggs, half a glass of carrot juice, green vegetables in abundance, liver and butter and, in addition a daily dose of 30 drops of a vitamin A preparation containing 25,000 international units per gram and "diachylon salicylicum ointment" locally. The patient visited me again fourteen days later. I found that her general condition had improved enormously; the skin of her face was clean, and in the mammary region only traces of scaling were to be seen.

Only the spinous follicular elevations on various symmetric areas, especially on the back, had not yet disappeared entirely, although they were greatly diminished.

The plaque on the scalp was clean and covered with regularly growing hairs about 1 cm. long.

COMMENT

Taking into consideration the observations of Frazier and Hu, who saw atrophy of the hair bulbs and cystic degeneration in persons with avitaminosis A, and the observations of Sweet and K'ang, who found horny papules in the pilosebaceous follicles,[1] one can assume a temporary alopecia caused by avitaminosis A as a direct sequel of such anatomic changes. The quick response of the hair follicles to vitamin A therapy can be compared with the usual quick disappearance of ocular lesions caused by vitamin A deficiency when the missing vitamin is given in abundance.

SUMMARY

A 40 year old woman in whom vitamin A deficiency had caused circumscribed alopecia and phrynoderma reported for treatment. Use of a diet rich in vitamin A and a preparation containing the concentrated vitamin during fourteen days cured the alopecia, almost completely cleared the skin and greatly improved the general condition.

1. Cited by Sutton, R. L., and Sutton, R. L., Jr.: Synopsis of Diseases of the Skin, St. Louis, C. V. Mosby Company, 1942.

HEPATOTOXIC ACTION OF ARSENICALS

EFFECT OF NEOARSPHENAMINE AND MAPHARSEN ON CHOLIC ACID SYNTHESIS AND USE OF DEHYDROCHOLIC ACID TO DIMINISH HEPATOTOXIC ACTION OF MAPHARSEN

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CHICAGO

This investigation was undertaken to determine (*a*) whether the intravenous administration of neoarsphenamine and mapharsen affects the synthesis of cholic acid and, if so, (*b*) whether the oral administration of dehydrocholic acid for three days prior to and after the administration of the arsenicals will diminish the hepatotoxic action of these arsenicals.

This study was stimulated by the clinical report that the administration of sodium dehydrocholate ameliorates arsenical hepatitis.[1] In a previous study [2] we attempted to ascertain the physiologic rationale of the claim, and found that sodium dehydrocholate did not increase the excretion of the arsenicals in the bile. In fact, sodium dehydrocholate tended to decrease and sodium glycocholate and sodium taurocholate tended to increase the excretion of arsenic in the bile. These tendencies were not statistically significant and could have been due to chance or random sampling. However, an increased excretion of arsenic is only one mechanism by which bile acids may serve to oppose the hepatotoxic action of arsenicals. For example, sodium dehydrocholate may counteract their hepatotoxic action by increasing the hepatic arterial blood flow,[3] which may be presumed to favor reparative processes or to render the liver less vulnerable to toxic agents.

The synthesis of cholic acid was chosen as an indicator of the hepatotoxic action of the arsenicals because it is well known to be decreased in the presence of hepatitis due to obstruction of bile ducts, infection or use of chloroform and to be reduced occasionally when drugs such as cinchophen and quinacrine hydrochloride are administered.[4]

We chose to administer preparations of dehydrocholic acid rather than sodium glycocholate and sodium taurocholate because the former do not significantly influence the synthesis or output of cholic acid in the bile.[5] Thus, should their administration prevent a depression of cholic acid synthesis due to mapharsen, the results should be less equivocal than if a bile salt containing cholic acid, such as sodium glycocholate, were given.

EXPERIMENTAL METHODS

Dogs with a permanent biliary fistula and a duodenal fistula for the return of bile were used. The surgical and experimental technics were the same as previously described for yielding the most quantitative results,[6] except that the bile was collected in a bag without continuous suction. The dogs were fed an equal portion of the daily ration every twelve hours. Since the quantity and quality of food ingested are important in a study of cholic acid output, the food intake was carefully controlled, and results were not included if the animal refused to consume any portion of the daily ration or if diarrhea developed. Since the dogs vomited after receiving mapharsen, the injections were given ten hours after the last meal in order not to interfere with the consumption and digestion of the meal.

The bile was collected at the same time each day and assayed for cholic acid by the method of Reinhold and Wilson.[7]

This study was aided in part by a grant from the Clara L. Abbott Fund.

From the Department of Physiology, Northwestern University Medical School.

1. Appel, B.: Sodium Dehydrocholate in Arsphenamine Poisoning, Arch. Dermat. & Syph. **27**:401 (March) 1933. Appel, B., and Jankelson, I. R.: Treatment of Arsenical Hepatitis with Sodium Dehydrocholate, ibid. **32**:422 (Sept.) 1935.

2. Annegers, J. H.; Snapp, F. E.; Ivy, A. C., and Atkinson, A. J.: The Effect of Bile Acids on the Biliary Excretion of Neoarsphenamine and Mapharsen, to be published.

3. Grodins, F. S.; Osborne, S. L.; Ivy, A. C., and Goldman, L.: The Effect of Bile Acids on Hepatic Blood Flow, Am. J. Physiol. **132**:375, 1941.

4. Annegers, J. H.; Snapp, F. E.; Paskind, L.; Ivy, A. C., and Atkinson, A. J.: Retention of Atabrine in Animal Body: Excretion in Bile and Urine and Effect on Cholic Acid Output, War Med. **4**:176 (Aug.) 1943. Annegers, J. H.; Snapp, F. E.; Atkinson, A. J., and Ivy, A. C.: Variations in Susceptibility to Cinchophen as Observed in Animals with Bile Fistulas, J. Lab. & Clin. Med. **28**:828, 1943.

5. Berman, A. L.; Snapp, F. E.; Ivy, A. C.; Atkinson, A. J., and Hough, V. S.: The Effect of Various Bile Acids on the Volume and Certain Constituents of Bile, Am. J. Digest. Dis. **7**:333, 1940.

6. Kocour, E., and Ivy, A. C.: The Effect of Certain Foods on Bile Volume Output Recorded by a Quantitative Method, Am. J. Physiol. **122**:325, 1938.

7. Reinhold, J. G., and Wilson, D. W.: Cholic Acid Determination, J. Biol. Chem. **96**:637, 1932.

When the effect of dehydrocholic acid was to be determined, the equivalent of 1.5 Gm. of this substance was given in the form of either sodium dehydrocholate or a mixture of oxidized bile acids consisting chiefly of dehydrocholic acid[8a] at twelve hour intervals for three days before and after the administration of the arsenical.

Neoarsphenamine was given intravenously in a single dose of 300 mg. (60 mg. of arsenic) and mapharsen in a single dose of 60 mg. (17.4 mg. of arsenic). Injection of an arsenical was not repeated more frequently than once a week. It was assumed that this was not too frequently because our previous study showed that arsenic disappeared from the bile within a week after the administration of such a dose.

The dose of mapharsen used, on the basis of body weight, is about twice the daily dose used in the intensive five day treatment of syphilis, the liver–body weight ratio being approximately the same in man and dog. A man weighing 70 Kg. and receiving a daily dose of 240 mg. obtains 3.4 mg. per kilogram; a dog weighing 10 Kg. and receiving a dose of 60 mg. obtains 6 mg. per kilogram. The L.D. 60 dose for dogs is 13 mg. per kilogram. The dose used was chosen with the idea of obtaining evidence of a hepatotoxic action without endangering the life of the animals.

In order to prevent the possibility of the results' being altered by the development of an immunity to repeated injections of the arsenicals, the injections of neoarsphenamine and mapharsen with and without dehydrocholic acid were alternated between the different dogs.

RESULTS

The Effect of Neoarsphenamine on Bile Formation.—Table 1 shows the results of 10 tests on 9 dogs in which the volume of bile and output of cholic acid, under the basal conditions of the diet alone, without an injection of neoarsphenamine, are compared with the output after an injection.

TABLE 1.—*Effect of 300 Mg. of Neoarsphenamine on Bile Volume and Cholic Acid Output During Twenty-Four Hours After Injection of the Drug*

	Bile, Cc.			Cholic Acid, Mg.		
Dog	Control	300 Mg. Neoarsphenamine	Percentage Change	Control	300 Mg. Neoarsphenamine	Percentage Change
C4	135	146	+ 8	1,379	955	−31
C7	129	127	0	1,944	1,313	−32
C7	129	181	+40	1,944	1,476	−24
D9	155	148	− 5	1,401	1,645	+17
F9	118	140	+19	1,433	1,690	+18
G5	150	162	+ 8	1,424	1,780	+25
G6	141	146	+ 3	1,285	1,446	+12
G9	134	141	+ 5	1,185	1,072	− 6
G10	89	84	− 6	853	816	− 4
H2	132	177	+34	1,097	982	−10
Average	131	145	+11	1,395	1,318	− 4

The average control twenty-four hour volume output was 131 cc. The output during the first twenty-four hours after the injection of 300 mg. of neoarsphenamine was 145 cc. The average increase in the volume output of bile was 11 per cent. On the basis of our previous experience with the bile fistula dogs, when the bile is collected in a bag a plus or minus 10 per cent variation in a group of tests occurs spontaneously under basal conditions. So it cannot be concluded that neoarsphenamine causes a choleresis. However, in 1 test on dog C 7 and in dog H 2 choleresis did occur.

TABLE 2.—*Effect of 60 Mg. of Mapharsen on Bile Volume and Cholic Acid Output During Twenty-Four Hours after Injection of the Drug*

	Bile, Cc.			Cholic Acid, Mg.			
Dog	Control	After Mapharsen	Percentage Change	Control	24 Hr. After Mapharsen	Percentage Change	24 to 48 Hr. After Mapharsen
G2	122	140	+15	1,752	1,232	−30	1,893
G3	217	227	+ 5	2,643*	2,133	−19	2,440
G5	150	145	− 3	1,425	552†	−61	913
G6	141	146	+ 3	1,285	830	−35	1,410
G6	120	116	0	1,152	267†	−77	580
G7	161	140	−13	1,902	1,428	−25	.....
G9	130	145	+11	1,105	915	−17	1,202
G10	98	87	−11	833	313†	−63	585
H2	143	171	+13	813	632†	−31	1,106
H3	131	156	+19	827	1,000	+17	1,280
Average	141	147	+ 4	1,384	940	−34 −32	1,157

$$\left[\frac{1,384 - 940}{1,384} = -32\right]$$

* This is an unusually large synthesis for a 12 Kg. dog.
† These are definitely abnormal yields.

The effect of the neoarsphenamine on synthesis of cholic acid was inconsistent. The average depression of 4 per cent is not significant. Since it is unusual for cholic acid synthesis to vary more than 25 per cent from day to day under basal conditions, we believe that the injection depressed cholic acid synthesis in 2 and possibly 3 tests, namely, in tests on dogs C 4 and C 7. In none of these tests was the output less than 800 mg. Previous experience has shown that hepatitis is present when the output is less than 800 mg. in dogs receiving our standard diet.

The Effect of Mapharsen on Bile Formation.—Table 2 shows the results of 10 tests on 9 dogs. The injection of 60 mg. of mapharsen produced no significant change in the volume output of bile. However the synthesis of cholic acid was decreased in 9 out of 10 tests. On the average, 34 per cent less cholic acid was synthesized during the twenty-four hour period after injection of mapharsen than in the three twenty-four hour periods before injection.

8a. The mixture of oxidized bile acids used was ketochol (G. D. Searle & Company).

Ordinary methods of statistical analysis did not show a significant difference. This result was due chiefly to the unusually high rate of synthesis of dog G 3. However, the odds are only 10 in 1,024 in favor of 9 depressions occurring by chance in 10 tests. Moreover, our experience with many bile fistula dogs during the past eight years teaches that when our standard diet is fed any basal synthesis below 800 mg. of cholic acid in dogs weighing 8 to 12 Kg. establishes the presence of hepatitis. The fact that the cholic acid output increased again during the second and third days after the injection is additional evidence that the mapharsen was the cause of the depression.

The Effect of the Oral Administration of Dehydrocholic Acid Before and After the Administration of Neoarsphenamine.—The results of 12 experiments on 12 dogs showed that dehydrocholic acid given orally before and after 300 mg. of neoarsphenamine yielded no significant changes in cholic acid synthesis. This might be anticipated, since the neoarsphenamine alone failed to cause a significant depression except in 2 tests.

The Effect of the Oral Administration of Dehydrocholic Acid Before and After the Administration of Mapharsen.—The results are shown in table 3; 10 tests were performed on 5 dogs.

TABLE 3.—*Effect of Feeding 1.5 Gm. of Dehydrocholic Acid Every Twelve Hours Before and After Injection of 60 Mg. of Mapharsen on Bile Volume and Cholic Acid Output During Twenty-Four Hours Following Injection of the Drug*

	Bile, Cc.			Cholic Acid, Mg.		
Dog	Control	After Mapharsen	Percentage Change	Control	After Mapharsen	Percentage Change
G5	247	287	+16	1,380	1,050	−24
G5	260	238	− 8	1,040	520*	−50
G6	228	265	+16	1,075	1,130	+10
G6	216	225	+ 5	1,190	665*	−44
G7	292	324	+11	2,395	1,830	−24
G8	251	301	+20	1,107	997	−10
G9	232	289	+25	1,439	1,760	+22
G9	242	283	+17	1,580	1,130	−28
G10	265	281	+ 5	902	945	+ 5
G10	231	252	+ 9	1,016	617*	−39
Average	246	275	+12	1,312	1,063	−18
						−19

$$\left[\frac{1{,}312 - 1{,}063}{1{,}312} = -19\right]$$

* These are definitely abnormal yields.

The average decrease in cholic acid synthesis in these tests was 18 per cent as compared with 34 per cent (table 2) when dehydrocholic acid was not administered. This difference appears to show that the bile acid offered definite protection. However, it should be noted that 3 of the animals showed definitely abnormal cholic acid outputs, as compared with 4 of the animals which did not receive dehydrocholic acid, and the difference is not statistically significant.

COMMENT

It is generally recognized that in animals mapharsen is about twelve times as toxic on the basis of weight as neoarsphenamine. Thus it is not surprising that we found 60 mg. of mapharsen to be more toxic to the liver, as judged by cholic acid synthesis, than 300 mg. of neoarsphenamine. If we had used a dose of 720 mg. of neoarsphenamine (12 × 60 mg.), it is likely, in view of the fact that 300 mg. caused evidence of hepatic damage in 2 of 9 dogs, that most dogs would have manifested temporary hepatic damage, as occurred with 60 mg. of mapharsen.

On the contrary, recent clinical literature indicates that neoarsphenamine is more hepatotoxic than the foregoing figures indicate. For example, Leifer, Chargin and Hyman [8] observed 382 patients with syphilis treated with 800 mg. of neoarsphenamine daily for five days and 240 mg. of mapharsen daily for five days. Jaundice occurred in 3.6 per cent of the patients given neoarsphenamine and in 0.7 per cent of those receiving mapharsen. Peripheral neuritis was also more frequent when neoarsphenamine was given. Sadusk and associates [9] gave the same dose of mapharsen to 33 patients for five days and observed no change in the icteric index and sulfobromophthalein clearance. And Levin and Keddie [10] found transitory jaundice to have been reported in only 0.2 per cent of 10,370 patients who had received various doses of mapharsen. Either the differences observed by Leifer and co-workers are fortuitous, or the results of toxicity studies on animals are not applicable to man, or the rate of excretion of the two arsenicals by the liver is the determining factor.

The rate of excretion is an important factor determining the toxicity of drugs. In a previous

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study[2] it was found that 40 per cent of the arsenic in mapharsen was excreted by the liver in forty-eight hours whereas seventy-two hours was required for the excretion of 40 per cent of the arsenic in neoarsphenamine when single doses of the drugs were given. Hence, when the two arsenicals are given intensively, it is probable that neoarsphenamine accumulates in the liver to a greater extent than mapharsen.

It should be reiterated that the depression of cholic acid synthesis caused by the injection of mapharsen was transitory and the rate of synthesis returned to normal not later than the third day after the drug was given (table 2).

The results of the oral administration of preparations of dehydrocholic acid were unfortunately indecisive. The depression of cholic acid synthesis was not reduced consistently or entirely prevented (compare table 2 with table 3). Even though dehydrocholic acid appeared to offer some protection of the liver from the hepatotoxic action of mapharsen when the results were compared with those for a control series deprived entirely of salts, it does not follow that an intact animal in which bile acids normally circulate will be similarly benefited by additional bile acids. If a more significant difference between the series with and without bile acid had occurred, further study would have been indicated.

We suspect that therapeutic doses of the arsenicals produce evident hepatic damage clinically only in patients with a reduced margin of safety in the liver. And it is possible that a disturbance of the liver predisposes to arsenical encephalopathy. Thus, it is our opinion that the hepatic function should be studied prior to intensive arsenotherapy and that all patients prior to receiving arsenotherapy should be given a diet which is known experimentally to affect favorably the resistance of the liver to poisons.[11] In regard to administration of bile salts, it would appear that if the diet contains adequate protein flow of bile should be adequate and the administration of a bile acid would be superfluous, unless the increased hepatic arterial flow may have a desirable effect. To provide insurance against the possible presence of diminished bile formation due to the depressing influence of a high carbohydrate intake or to the presence of extremely viscous bile in some of the smaller biliary ducts, the use of bile salts is indicated. Otherwise, there is no clear rationale known for the use of bile salts in arsenotherapy.

CONCLUSION

A dose of 300 mg. of neoarsphenamine does not consistently depress cholic acid output in dogs with a permanent biliary fistula.

Mapharsen in a dose of 60 mg. consistently depresses cholic acid output in biliary fistula dogs deprived of bile acids.

Oral administration of dehydrocholic acid may aid in counteracting the hepatotoxic action of mapharsen.

It is suggested that patients scheduled to receive intensive arsenotherapy should have the function of their liver examined by one of the more sensitive tests (e. g., the 5 mg. sulfobromophthalein test) and be given a diet known to affect favorably the resistance to poisons for two or three days prior to the initiation of the therapy.

303 East Chicago Avenue.

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DETERMINATION OF MACROCYTIC ANEMIA AS AN AID IN DIAGNOSIS OF CERTAIN DEFICIENCY DERMATOSES

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WITH THE TECHNICAL ASSISTANCE OF LUCILLE LEVENTHAL
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In man, nutritional deficiencies of the various fractions of the B complex except thiamine are usually multiple; one or two symptoms are frequently present long before a fully developed disease syndrome makes its appearance. Examples of this limited effect are seen in cheilosis, greasy desquamation of the nasolabial folds, vascularization of the cornea which occurs in ariboflavinosis,[1] stomatitis, gastritis, dermatitis, diarrhea and constipation which often occur singly in niacin deficiency[2] and the nonpellagrous dermatoses such as those reported by Gross.[3]

In the experimental animal, changes involving the various tissues may be produced at will by withholding one or more of the various fractions of the B complex. These changes may be produced in the gastrointestinal tract, the nervous system, the hemopoietic system and the skin.

There are only two fractions of the B complex, niacin and riboflavin, which are known to affect cutaneous changes in man. All other dermatoses resulting from the absence of this essential component of the diet must be the effect of the lack of the unidentified fractions or of biotin or folic acid and others which at this time have not been sufficiently investigated.

Castle,[4] Harris[5] and others have pointed to the close similarity between the known deficiency diseases, pernicious anemia, pellagra and sprue. The major symptoms in each are different, yet in each there are often found identical symptoms. In pellagra, which differs from pernicious anemia and sprue by the constant involvement of the skin, macrocytic anemia is often encountered.

Ruffin and Smith[6] and Spies[7] have reported on the beneficial effect of liver extract on the gastrointestinal symptoms and anemia of pellagra. Goldsmith[8] has observed patients with chronic nutritional deficiency but without the clinical picture of pellagra who showed a severe macrocytic anemia and who responded to liver extract.

Hematologic studies were made on 179 patients with various dermatoses (table 1). The hematocrit value, the mean corpuscular volume and the mean corpuscular hemoglobin concentration indexes were determined according to the

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6. Ruffin, J. M., and Smith, D. T.: Treatment of Pellagra with Certain Preparations of Liver, Am. J. M. Sc. **187**:512-521 (April) 1934.

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method of Wintrobe.[9] Repeated examinations were done, when possible, on those patients showing wide variations from normal and those for whom a clinical diagnosis of deficiency dermatitis was made. As treatment progressed, additional examinations of the blood were performed.

TABLE 1.—*Incidence of Macrocytic Anemia in Patients with Various Dermatoses*

Disease	Total No. of Patients	With Macrocytic Anemia	
		Number	Per Cent
Erythematous dermatitis of head, neck and shoulders	11	10	91
Nonpellagrous eruptions of wide distribution	31	16	52.3
Ariboflavinosis	11	1	0.9
Photosensitization	4	0	0
All other dermatoses	122	29	23.8

There were 42 patients who complained of cutaneous lesions which did not conform to any dermatologic entity. For 31 of these a diagnosis of dermatitis resulting from deficiency was made on the basis of the objective cutaneous symptoms in addition to the presence of changes in the mucosa of the mouth, the existence of constipation or diarrhea, evidence of xeroderma, follicular keratotic plugging, brittle nails, keratosis of the conjunctiva, fissures of the oral commissures and a history of inadequate diet. In no instance was a diagnosis of pellagra supported by the results of examinations.

Fifty-two per cent of this group were found to have an increase in the mean corpuscular volume. These patients responded at once to proper dietary measures and parenteral injections of liver extract. The finding of macrocytic anemia in this group was an aid in establishing a diagnosis for slightly over one half. The conditions observed on physical examination and the dermatologic evaluation of the patient were the most important factors. Liver therapy was effective in bringing about a clinical cure in each instance. The mean corpuscular volume in all cases returned to normal.

TABLE 2.—*Hematologic and Clinical Observations at Time of Diagnosis*

Case	Sex	Age	Red Blood Cells	Hb (Sahli) Gm.	MCV	MCHC	Dermatitis
1	F	37	3.8	11	110	26	Neck, face
2	F	48	3.5	13	142	25	Neck, face, hands
3	F	48	4.3	14	102	31	Neck, face
4	M	60	4.5	13	132	21	Neck, arms, legs
5	F	58	3.2	13.5	131	32	Neck, face, ears
6	F	53	5	13	109	28	Neck, face
7	F	59	4.1	12.5	112	27	Neck, face, hand
8	F	50	4.4	13	105	28	Neck, axillary folds
9	F	45	3.6	12.5	113	30	Neck, arms
10	F	57	4.7	14.5	110	28	Neck, ankle
11	F	39	4.2	12	84	33	Neck, axillary folds

There were 11 patients who presented similar cutaneous lesions, 91 per cent of whom had macrocytic anemia (table 2). Response to parenteral injection of crude liver extract produced immediate improvement in the symptoms of pruritus and dermatitis and an early return in the size of the erythrocytes to normal (table 3). One patient whose dermatitis proved resistant ultimately yielded to continuous injections of crude liver extract (case 7). In case 8 the cutaneous symptoms failed to respond to crude liver extract, pyridoxine, calcium pantothenate and whole vitamin B complex administered parenterally as well as dilute hydrochloric acid, a high vitamin diet and massive doses of all vitamins administered by mouth. The blood picture changed from that of a macrocytic anemia to that of a simple microcytic type.

TABLE 3.—*Hematologic and Clinical Observations Following Parenteral Injections of Crude Liver Extract*

Case	Sex	Age	Red Blood Cells	Hb (Sahli) Gm.	MCV	MCHC	Dermatitis
1	F	37	4.6	13.5	95	30	Clear
2	F	48	4.9	14.5	96	30	Clear
3	F	48	4.9	13	91	28	Clear
4	M	60	4.9	13.5	94	29	Clear
5	F	58	4.6	13.5	95	29	Clear
6	F	53	4.4	13	89	33	Clear
7	F	59	5.2	12	84	27	Improved
8	F	50	5.3	13.5	74	34	Improved
9	F	45	4.5	11.5	83	30	Clear
10	F	57	5.4	15.5	87	32	Clear

These observations indicate that a clinical syndrome consisting of dermatitis and macrocytic anemia, resulting from a deficiency of fractions of the B complex present in liver extract, exists.

The cutaneous lesions in the early stages consisted of evanescent, patchy or diffuse, superficial, pruritic, scaly, dry or vesicular erythroderma. In the later stages the patches, which lost their evanescent character, became confluent and the vesiculation tended to disappear. The skin became edematous and slightly thickened.

In all cases the lesions were distributed on the sides of the neck, the face, the anterior part of the shoulders, the upper part of the chest and the areas immediately adjacent to the anterior axillary folds. Five patients presented lesions of similar character on the extremities. There was an imperfect symmetry of the lesions, one side usually being more involved than the other. The patients complained of intense itching.

9. Wintrobe, M. M.: The Volume and Hemoglobin Content of the Red Blood Corpuscle: Simple Method of Calculation, Normal Findings and Value of Such Calculations in the Anemias, Am. J. M. Sc. **177**:513-523 (April) 1929.

The series is composed of 10 women and 1 man. All came from the middle or upper economic levels. All declared that they ate an ample amount of food or enough to satisfy the appetite. Specific questioning invariably revealed poor dietary habits and inadequate consumption of food. Two patients were thin and underweight; 1 was greatly overweight, and in the others the weight was normal. All complained of mild mental depression, apprehension and fatigue. One patient was first seen in a ward for patients with mental disease. The others had been able to carry on their usual duties. The ages varied from 35 to 60.

All patients had been under the care of other physicians, and most of them were taking some form of vitamin therapy by mouth. One patient (case 1) had experienced fissures of the commissures of the mouth at the time of the onset of the dermatitis. Riboflavin, which had been prescribed by her family physician, produced an immediate healing of the oral lesions without altering the pruritic erythroderma of the neck. There was a tendency to spontaneous remissions and recurrences in cases 1, 2, 4, 5, 6 and 8.

A general xeroderma was present in 2 cases. Except for the presence of hyperglycemia in 1 instance, there were no evidences of metabolic disease. Symptoms referable to the gastrointestinal tract, except loss of appetite, were not found. Koilonychia was present in case 4.

In 10 cases the study of the blood revealed a mild reduction of the erythrocytes, and increase in the mean corpuscular volume and a decrease in the mean corpuscular hemoglobin concentration (table 2). The leukocytes for the most part were found to be in the lower range or below normal. In 1 case in which typical clinical symptoms of the skin were presented there was a normal blood picture (case 11).

Gastric analysis was possible in 2 cases, and each revealed an absence of free hydrochloric acid and low total acidity.

REPORT OF CASES

CASE 1.—J. A., a woman aged 37, a teacher, consulted me on April 5, 1943, complaining of a dermatitis and severe itching of the cheeks, neck, eyebrows and eyelids. The disease had its onset in December 1942 as a patchy dermatitis of the neck and fissures of the commissures of the mouth.

Riboflavin, which she had taken in adequate doses for five months, produced healing of the commissural lesions but had no effect on the dermatitis of the face and neck. Since the onset two spontaneous remissions of the dermatitis had occurred, each followed by an attack of greater intensity.

The patient's general health had been good. Her weight had increased slowly over a period of years. She considered herself to be in good health. She had had no abnormal gastrointestinal symptoms. Her menses were normal. She said that she had a good appetite, but on inquiry as to the specific foods, it was found that the total diet was unbalanced and inadequate, consisting of one full meal a day. The past history was noncontributory, except for an appendectomy which was performed in 1938.

Dermatologic examination of the patient revealed superficial, erythematous, vesicular, pruritic patches of dermatitis varying from 1 to 4 or 5 cm. in diameter on the sides of the neck and on the cheeks, supraorbital area and eyelids. The mucosa of the mouth was pale. Bitot spots were present in both eyes.

Because of the character of the lesions at the time of the original examination, a diagnosis of contact dermatitis was made. Use of all cosmetics, including finger nail lacquer, also soap and soap powders, was stopped. At the end of ten days, no improvement had occurred.

Laboratory examination of the blood on April 16, 1943 revealed the following values: white blood cell count 5,834, red blood cell count 3,867,000, hemoglobin content (Sahli method) 11 Gm., mean corpuscular volume 110 cubic microns, mean corpuscular hemoglobin 28 micromicrograms and mean corpuscular hemoglobin concentration 26 per cent. The color index was 0.85, saturation index 0.75 and volume index 1.2. A differential count was within normal limits. The blood smear showed anisocytosis with the predominance of macrocytes, poikilocytes and hypochromasia. The basal metabolic rate was —11 per cent.

Because of the history of an inadequate diet, a low hemoglobin content and an increased mean corpuscular volume, the patient was given a balanced diet, dilute hydrochloric acid by mouth, 150,000 U. S. P. units of vitamin A daily and ferrous sulfate by mouth. In addition, 3 cc. of crude liver extract containing 2 hemopoietic units per cubic centimeter was given intramuscularly twice weekly.

The subjective symptoms of itching disappeared promptly, and the lesions began to fade immediately. Examination of the blood which was made five weeks after treatment had been administered revealed normal values. When the patient was seen for the last time, on May 29, 1943, she was free of all evidence of disease. One year later there had been no recurrence.

CASE 2.—O. M., a 48 year old housewife, consulted me for the first time in July 1940, with an acute vesicular dermatitis of the backs of the hands. A tentative diagnosis of contact dermatitis was made. The condition cleared quickly under soothing applications. A recurrence in January 1941 responded to the same treatment.

The third attack occurred in October 1941, as an acute vesicular dermatitis of the hands, arms, neck and nasolabial folds. Fissures were present in the commissures of the mouth. The tongue was smooth and livid. The history, which was otherwise unimportant, revealed a prolonged period of inadequate diet. The chief complaint was intense itching of the involved areas.

Laboratory examination of the blood in October 1941 revealed the following values: white blood cell count 6,834, red blood cell count 3,520,500, hemoglobin content (Sahli method) 13 Gm., mean corpuscular volume 142 cubic microns, mean corpuscular hemoglobin 37 micromicrograms and mean corpuscular hemoglobin concentration 25 per cent. The color index was 1, saturation index 0.8 and volume index 1.5. A differential count was within normal limits. The blood smear showed macrocytosis and poikilocytosis.

Because of the history of an inadequate diet and the hematologic values, the patient was placed on a balanced diet and orally she was given vitamin B complex (concentrated extract of liver and yeast, containing thiamine) with liver capsules (concentrated extract of beef liver and the anti-pernicious-anemia factor with ferrous sulfate), 150,000 U. S. P. units of vitamin A daily and 9 mg. of riboflavin daily. In addition, 3 cc. of crude liver extract containing 2 hemopoietic units per cubic centimeter was given intramuscularly twice weekly for a period of three months.

There was improvement generally, with healing of the fissures in the commissures of the mouth. Examination of the blood which was made three months after therapy had been instituted revealed all values within the normal range. The patient discontinued treatment.

In August 1943, two years later, the patient consulted me for the fourth time, complaining of a recurrence of the lesions of the skin of the backs of the hands and fissures in the commissures of the mouth. The tongue was red, slick and fissured. Examination of the blood at that time revealed the following values: red blood cell count 3,762,500, hemoglobin content (Sahli method) 11.5 Gm., mean corpuscular volume 110 cubic microns, mean corpuscular hemoglobin 31 micromicrograms and mean corpuscular hemoglobin concentration 28 per cent. The color index was 0.9, saturation index 0.8 and volume index 1.2. The blood smear showed anisocytosis and poikilocytosis.

The patient was placed under treatment but disappeared from my observation.

Case 3.—T. F., a woman aged 48, a housewife, consulted me in July 1941, complaining of a pruritic dermatitis of the face, neck and eyelids which had been present for one month. A tentative diagnosis of contact dermatitis was made, and the patient was instructed to discontinue use of all cosmetics, soap and soap powder. At the end of two weeks no improvement had occurred. On further questioning, the patient stated that she had been on a reducing diet. She also gave a history of the dermatitis becoming worse after exposure to the sun. The menses had stopped normally four years before. The patient complained of constipation. The past history was essentially noncontributory.

Dermatologic examination revealed an erythematous, superficial, vesicular, diffuse dermatitis which was present on the eyelids, nose, chin, cheeks and neck. The nails were pale and splitting. The tongue was pale. The rest of the body was free of dermatitis.

Laboratory examination of the blood in July 1941 revealed the following values: white blood cell count 6,032, red blood cell count 4,370,500, hemoglobin content (Sahli method) 14 Gm., mean corpuscular volume 102 cubic microns, mean corpuscular hemoglobin 34 micromicrograms and mean corpuscular hemoglobin concentration 31 per cent. The color index was 0.95, saturation index 0.93 and volume index 1.1. A differential count was within normal limits. The blood smear showed macrocytosis. The basal metabolic rate was + 5 per cent. The urine was normal.

As the result of the condition of the blood and the history of an inadequate diet, the patient was placed on a balanced diet, and vitamin A, 150,000 U. S. P. units daily by mouth, and parenterally 3 cc. of crude liver extract containing 2 hemopoietic units per cubic centimeter, was given twice weekly.

Treatment was continued for a period of two months, after which time the cutaneous lesions had healed. The hematologic values at that time were within normal limits.

Case 4.—M. J., a 60 year old salesman, consulted me in February 1941 regarding an intensely pruritic dermatitis of the right ankle, toes, legs, scrotum, perineum, arms and neck. With local therapy, the lesions improved.

In October of the same year, the patient returned with a recurrence of the dermatitis. Examination revealed a widespread erythroderma, involving the neck, arms, legs, ankles, scrotum and perineum. He complained of intense itching. The rest of the body was free of lesions except for the presence of spooning of the finger nails. There also was noted a general though vague depression and anxiety. The patient was very thin.

Laboratory examination of the blood in October 1941 revealed the following values: white blood cell count 5,824, red blood cell count 4,504,000, hemoglobin content (Sahli method) 13 Gm., mean corpuscular volume 132 cubic microns, mean corpuscular hemoglobin 28 micromicrograms, mean corpuscular hemoglobin concentration 21 per cent. The color index was 0.84, saturation index 0.74 and volume index 1.3. The differential count was within normal limits. The blood smear showed poikilocytosis, hypochromasia and anisocytosis with predominance of macrocytes. The urinalysis revealed essentially normal values.

Because of the history and the hematologic values, the patient was given liver and iron capsules by mouth, also dilute hydrochloric acid and later B complex with liver. He was placed on a well balanced diet and given intramuscularly 2 cc. of crude liver extract containing 2 hemopoietic units per cubic centimeter two or three times a week.

Under treatment the patient gained in weight, his dermatitis disappeared and his general well-being was improved. After six weeks of intensive treatment, the hematologic values were within normal limits.

Case 5.—H. P., a 58 year old housewife, consulted me in August 1942, complaining of an itchy dermatitis of the ears, occipital region and perianal region which had been present for six months. The general health had been good except for constant worry and nervous tension. She had a clinical recovery with local applications, sedatives and roentgen ray treatments.

In April 1943 she returned with an acute dermatitis of the face, neck, scalp, ears and eyelids accompanied by intense itching. She gave a history of poor appetite and eating sporadically.

Laboratory examination of the blood in April 1943 revealed the following values: white blood cell count 9,550, red blood cell count 3,290,000, hemoglobin content (Sahli method) 13.5 Gm., mean corpuscular volume 131 cubic microns, mean corpuscular hemoglobin 42 micromicrograms and mean corpuscular hemoglobin concentration 32 per cent. The color index was 1.2, saturation index 1 and volume index 1.4. The differential count was within normal limits. The Kahn reaction of the blood was negative. The urine was normal.

The patient was given liver and yeast extract by mouth, also riboflavin, dilute hydrochloric acid and vitamin A, 150,000 U. S. P. units per day. She was placed on a balanced diet. Intramuscularly, she was given 2.5 cc. of crude liver extract containing 2 hemopoietic units per cubic centimeter every two days.

In January 1944 the hematologic values were within normal range and the patient had improved generally and there were no objective symptoms. She had one slight recurrence of the dermatitis which cleared with injections of liver extract.

Case 6.—C. G., a woman aged 53, a seamstress, consulted me in November 1943, complaining of a pruritic, erythematous dermatitis of the chin, cheeks, sides and

anterior surface of the neck and upper pectoral area of the chest which had been present for six weeks. She gave a history of having had a "nervous stomach" for years, an insufficient diet, lack of appetite, nausea and diarrhea, loss of weight and periods of moderately severe mental depression. She was pallid. The past history was noncontributory except for a nervous breakdown which she had had five years prior to the present illness.

The cutaneous eruption consisted of superficial patches of erythematous dermatitis, some of which were covered with a fine desquamation. The size of the patches varied from 0.5 to 3 or 4 cm. in diameter. The edges were not sharply defined.

The laboratory examination of the blood in November 1943 revealed the following values: red blood cell count 5,040,000, hemoglobin content (Sahli method) 13 Gm., mean corpuscular volume 109 cubic microns, mean corpuscular hemoglobin 26.4 micromicrograms and mean corpuscular hemoglobin concentration 28.6 per cent. The color index was 0.76, saturation index 0.89 and volume index 1.

The patient was placed on a well balanced diet, and 3 cc. of crude liver extract containing 2 hemopoietic units per cubic centimeter was given parenterally twice weekly. In December 1943, after one month's treatment, the dermatitis had cleared. The hematologic values at that time were within normal limits, with the exception of a slight reduction in the red blood cell count. The injections of liver extract were discontinued, but the patient was instructed to take liver extract by mouth. She admitted an improvement in her general feeling of well-being.

The patient remained well until March 1944, when she suffered a recurrence of the dermatitis on the sides of the neck and face. She stated that she had become emotionally upset, had lost her appetite and had been nauseated for the past two months. She had continued taking the liver extract by mouth.

Examination of the blood at this time showed the following values: red blood cell count 3,990,000, hemoglobin content (Sahli method) 13 Gm., mean corpuscular volume 103 cubic microns, mean corpuscular hemoglobin 32 micromicrograms and mean corpuscular hemoglobin concentration 31 per cent. A gastric analysis made at this time showed no free hydrochloric acid and a total acid of 6 per cent.

Parenteral injections of liver and dilute hydrochloric acid by mouth produced a rapid return of all signs to normal.

CASE 7.—R. U., a woman aged 59, a delicatessen operator, consulted me in January 1944, complaining of an itchy dermatitis of the sides of the neck which had had its onset in October 1943. She said that there had been three partial remissions of the dermatitis after the onset. She had a fair appetite but was too busy to eat. Her general health had been good. She complained of constipation.

Examination of the skin revealed an erythematous, squamous, pruritic dermatitis of the sides of the neck, on the chest (fig. 1), about the lips, on the chin and on the right hand and wrist. The tongue was gray and spotted.

Examination of the blood showed the following values: white blood cell count 7,650, red blood cell count 4,162,500, hemoglobin content (Sahli method) 12.5 Gm., mean corpuscular volume 112 cubic microns, mean corpuscular hemoglobin 30 micromicrograms and mean corpuscular hemoglobin concentration 27 per cent. The color index was 0.89, saturation index 0.86 and volume index 1.2. The differential count was within normal limits. The blood smear showed anisocytosis, with macrocytes predominant and poikilocytes. The Kahn reaction of the blood was negative.

The patient was placed on a well balanced diet and was given dilute hydrochloric acid by mouth. In addition, 3 cc. of crude liver extract containing 2 hemopoietic units per cubic centimeter was given parenterally twice a week. Later the patient was given B complex, nikethamide, calcium pantothenate and nicotinamide combined with the crude liver extract parenterally, without accelerating the clinical progress.

After five weeks of treatment, the blood count revealed the following values: red blood cell count 5,233,500, hemoglobin content (Sahli method) 12 Gm., mean corpuscular volume 84 cubic microns, mean corpuscular hemoglobin 23 cubic micromicrograms and mean corpuscular hemoglobin concentration 27 per cent. The color index was 0.67, saturation index 0.89 and volume index 1. The cutaneous lesions showed improvement; all areas were fading, and the patient had gained in weight, was less tired and felt more ambitious. Under continuous administration of crude liver extract, the skin returned to normal.

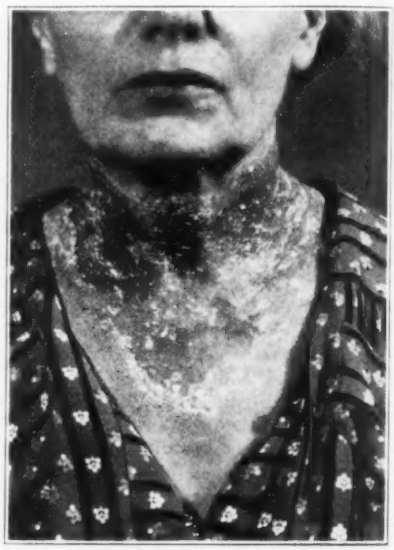

Fig. 1 (case 7).—Diffuse squamous dermatitis of the neck and chest.

CASE 8.—K. D., a woman aged 50, a stenographer, consulted me in October 1941, complaining of a pruritic dermatitis of the lips, eyelids and left side of the neck. A diagnosis of contact dermatitis was made at this time. With roentgen ray treatments and stopping use of cosmetics, the dermatitis disappeared. In January 1942 she had a recurrence of the dermatitis on the sides of the neck, which responded to local therapy and removal of cosmetics. In October 1943 she had a recurrence of the dermatitis for the third time, which failed to respond to treatment. At this time the lesions resembled neurodermatitis, and the patient was given mild sedatives.

In January 1944 a diagnosis of deficiency disease was made. Examination of the cutaneous lesions at that time revealed a patchy superficial erythematous, squamous, dry pruritic dermatitis of the sides of the neck, over the pectoral area and in the anterior axillary folds. Fissures were present in the commissures of the

mouth. The patient gave a history of dieting to reduce weight.

Examination of the blood in January 1944 revealed the following values: white blood cell count 6,816, red blood cell count 4,442,500, hemoglobin content (Sahli method) 13 Gm., mean corpuscular volume 105 cubic microns, mean corpuscular hemoglobin 29 micromicrograms and mean corpuscular hemoglobin concentration 28 per cent. The color index was 0.86, saturation index 0.89 and volume index 1.1. The differential count was within normal limits. The blood smear showed macrocytosis and poikilocytosis. Gastric analysis showed no free hydrochloric acid.

The patient was given a well balanced diet, liver extract and dilute hydrochloric acid by mouth and parenterally crude liver extract containing 2 hemopoietic units per cubic centimeter, the dose starting at 1 cc. and being increased to 4 cc. per injection, twice weekly. In conjunction with the crude liver extract, calcium pantothenate and nicotinamide were also administered.

Examination of the blood after two months of treatment with parenteral injections of liver extract revealed a decrease in the mean corpuscular volume from 105 to 74 cubic microns. At the same time the mean corpuscular hemoglobin concentration increased from 28 to 34 per cent. This shift in the blood picture indicated that the anemia had changed from a macrocytic type to a simple microcytic type. The patient did not cooperate to the extent of eating a full diet. The cutaneous lesions failed to heal entirely. This case must be classified as a clinical failure.

Case 9.—A. B., a 45 year old housewife, was admitted to the neurologic division of St. Mary's Hospital in St. Louis in September 1942, at which time her chief complaint was dry and scaly skin of five weeks' duration, generalized weakness, especially in the legs, gradual loss of memory and an inability to think clearly of about two weeks' duration and emotional instability during the past several weeks. A diagnosis of toxic cerebritis and avitaminosis was made by the attending psychiatrist.

Because of an acute dermatitis which had developed during the period of hospitalization, dermatologic consultation was sought in October 1942. Examination revealed an acute erythematous dermatitis of the forehead, nasolabial folds, ears, neck, shoulders and arms. All other areas of the skin were dry and rough. The tongue was thick and dry but not denuded. She gave a history of having a poor appetite and an inadequate diet. Itching was a distressing symptom.

While in the hospital, the patient had been given a high caloric high vitamin diet and thiamine hydrochloride (10 mg.) by mouth; 300 mg. of nicotinic acid was given intravenously, and nicotinic acid and riboflavin were administered by mouth. With this therapy the mental symptoms improved, but there was no change in the dermatologic findings.

Laboratory examination of the blood in October 1942 revealed the following values: white blood cell count 8,275, red blood cell count 3,670,500, hemoglobin content (Sahli method) 12.5 Gm., mean corpuscular volume 113 cubic microns, mean corpuscular hemoglobin 34 micromicrograms and mean corpuscular hemoglobin concentration 30 per cent. The color index was 1, saturation index 0.95 and volume index 1.2. The differential count was within normal limits. The blood smear showed anisocytosis and poikilocytosis. The Kahn reaction of the blood was negative.

The patient was given vitamin A, 150,000 U. S. P. units daily by mouth, and 3 cc. of crude liver extract containing 2 hemopoietic units per cubic centimeter was given intramuscularly twice weekly. Later, vitamin B complex and liver extract were administered by mouth.

After five weeks of intensive treatment, examination of the blood revealed the following values: red blood cell count 4,542,000, hemoglobin content (Sahli method) 11.5 Gm., mean corpuscular volume 83 cubic microns, mean corpuscular hemoglobin 25 micromicrograms and mean corpuscular hemoglobin concentration 30 per cent. The indexes were at normal levels. The cutaneous lesions had greatly improved, and the itching had subsided.

Treatment was continued for an additional four months. At the end of this period the lesions of the skin had disappeared entirely and the patient had regained her normal mental and emotional balance.

Case 10.—W. H., a 57 year old housewife, consulted me in July 1943, complaining of an itchy dermatitis of the sides of the neck which had been present for several weeks. A chronic, thickened, pruritic dermatitis of one year's duration was present on the dorsum of the left foot.

She had suffered from diabetes mellitus since 1934. She had been obese for many years and gave a history of having reduced from 270 to 200 pounds (122.5 to 90.7 Kg.) with the aid of thyroid (10 grains [0.65 Gm.] daily) and diet. Her weight at the time she was first seen was 230 pounds (104.3 Kg.).

She was under the care of Dr. Samuel B. Grant, who reported the presence of vascular hypertension (200 systolic and 120 diastolic). Blood sugar levels varied from 231 to 143 mg. per hundred cubic centimeters. Sugar did not appear in the urine unless the blood sugar level was over 200 mg.

In March 1943 the patient began a reducing diet, which produced a change in weight from 233½ to 217½ pounds (106 to 98.7 Kg.) by August 1943. At this time the diet was supplemented by two multiple vitamin capsules daily. It was during the period in which she was on a reducing diet supplemented with vitamin capsules that an acute dermatitis developed on the sides of the neck.

Dermatologic examination of the lesions revealed a dry, scaly, pruritic dermatitis on the sides of the neck and a dry, thickened, scaly, pruritic dermatitis on the dorsum of the left foot.

Laboratory examination of the blood revealed the following values: white blood cell count 9,225, red blood cell count 4,775,000, hemoglobin content (Sahli method) 14.5 Gm., mean corpuscular volume 110 cubic microns, mean corpuscular hemoglobin 30 micromicrograms and mean corpuscular hemoglobin concentration 28 per cent. The color index was 0.9, saturation index 0.83 and volume index 1.2. The differential count was within normal limits.

The patient was given a well balanced diet and vitamin B complex by mouth, and 1.5 to 3 cc. of crude liver extract containing 2 hemopoietic units per cubic centimeter was given intramuscularly twice weekly. At the end of two months' treatment, the lesions of the skin had disappeared and the hematologic values were within normal limits.

Case 11.—R. C., a woman aged 39, a bookkeeper, consulted me in March 1944, complaining of an itchy dermatitis of the sides of the neck which was of four days' duration. The original attack had appeared about two months previously. The patient stated that she had no desire to eat and that she was nervous and a poor sleeper. She lived alone and prepared her own meals. The diet was deficient in meat and eggs. She had had

no gastric upsets. She said that she had had erythema multiforme when a child and two major operations within the past fifteen years. For the past two years, to avoid indigestion, she had taken sodium bicarbonate after each meal.

Examination of the cutaneous lesions revealed dry, scaly, pruritic, round and oval patches of dermatitis on the sides of the neck (fig. 2), the supraclavicular areas, the anterior surface of the chest and the arms adjacent to the axillary folds. The tongue appeared normal in color. The mucosa of the mouth was normal. The nails were brittle but normal in shape. There were Bitot spots present in both eyes.

Examination of the blood revealed the following values: white blood cell count 8,882, red blood cell count 4,237,500, hemoglobin content (Sahli method) 12 Gm., mean corpuscular volume 84 cubic microns, mean corpuscular hemoglobin 28 micromicrograms and mean corpuscular hemoglobin concentration 33 per cent. The indexes were normal, and the differential count was within normal limits.

Fig. 2.—Lesions characteristic of the early stages.

The patient was given 150,000 U. S. P. units of vitamin A daily by mouth and 2.5 cc. of crude liver extract containing 2 hemopoietic units per cubic centimeter was given intramuscularly twice weekly. She was placed on a well balanced diet. After two weeks' treatment, the itching stopped and the lesions healed.

DIFFERENTIAL DIAGNOSIS

The objective observations and the symptoms of severe pruritus made the differential diagnosis between nutritional dermatitis and contact dermatitis extremely difficult. The determination of the existence of macrocytic anemia in these patients was the only evidence, except a history of inadequate diet, to support or confirm the clinical impression. Once the presence of macrocytic anemia was established, treatment of a specific nature with crude liver extract produced rapid results.

Sensitization to actinic rays, on exposure to light, results in dermatitis of the exposed skin. This factor, while possibly present to some degree, as in other deficiency diseases, such as pellagra, was not considered as a major etiologic agent. The onset of the disease in these patients, who were all indoor workers, was in the wintertime in 8 cases. There was no direct exposure to the sun. The disease occurred on the covered parts also. Five patients for whom the diagnosis of photosensitization not induced by topical sensitizing agents was made had normal hematologic values and did not respond to parenteral injection of liver extract.

The difference in objective signs, the absence of macrocytic anemia in 6 patients with cheilosis which responded to riboflavin and the failure of riboflavin to influence the dermatitis in case 1 were sufficient to exclude ariboflavinosis from consideration.

Seborrheic dermatitis was eliminated from consideration because the dermatologic criteria necessary for such a diagnosis were not present.

A similarity in clinical findings seemed to link these cases with some of those which were observed by Gross [3] and reported as cases of nonpellagrous eruptions due to deficiency of vitamin B complex. Of the larger group, 31 cases, in which a diagnosis of deficiency dermatitis was made, many fell into the five classifications which he enumerated.

In addition, 126 persons, including 15 with acne, 12 with contact dermatitis, 4 with eczema, 8 with dermatitis herpetiformis, 5 with lichen planus, 20 with neurodermatitis, 6 with lupus erythematosus, 10 with psoriasis and 1 to 4 each with nineteen other dermatologic diseases were examined. Twenty-four per cent were found to have an increase in the mean corpuscular volume, and 7 per cent had microcytic hypochromic anemia.

SUMMARY AND CONCLUSIONS

Hematologic studies were performed on 179 patients presenting various dermatologic diseases with a view to determine the presence of macrocytic anemia, especially in persons in whom a deficiency of one or more fractions of the vitamin B complex was presumed to be a causative agent.

Forty-two patients presented lesions which did not conform to any dermatologic entity. Thirty-one of this group were ultimately classified as having eruptions which were due to vitamin B complex deficiency. Determination of the mean volume of the red cells proved to be an aid in the diagnosis in 22 (52 per cent) of these cases.

The response of the clinical symptoms, the improvement in the patients' general well-being and the drop in the mean corpuscular volume in all instances as a result of the parenteral injection of crude liver extract led to the conclusion that these patients present a syndrome of dis-

ase which is, at least in part, a result of a nutritional deficiency. The deficient substance is present in liver extract.

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ABSTRACT OF DISCUSSION

DR. DUDLEY C. SMITH, Charlottesville, Va.: Vitamin B complex is, as its name implies, made up of many factors. It was already known that deficiencies in this nutritional complex cause many variable clinical and laboratory syndromes. There is presented in this paper another type of cutaneous abnormality associated with hematologic changes resulting from deficiency in some fraction or fractions of this mixture. It would be an interesting problem to determine the exact detailed fraction or fractions involved. This preliminary report by Dr. Stryker and his associate does not attempt to solve this detail. Do the essayists have any opinion on this phase of the subject? It may be that the fraction which causes the cutaneous change is different from the fraction which causes the blood abnormality. It certainly would seem to be different from the hemopoetic factor that is used for pernicious anemia, because the response to crude liver extract is better than that to the purified extract.

The pruritic erythroderma described resembles clinically a contact or irritative dermatitis. How many errors in diagnosis have we made in the past. The majority of cases with this skin picture is probably due to external irritation. Does this deficiency state make the skin more susceptible to irritation or does the lack of this fraction produce per se the skin inflammation? If the skin is made more susceptible to irritation by this deficiency, then we may have a basic explanation for cutaneous contact allergy.

Simple laboratory tests for avitaminoses are not numerous. The association of a macrocytic anemia with the dermatosis described increases the possibility of accuracy in diagnosis. However, macrocytic anemia is also associated with other types of nutritional deficiency. The macrocytic anemias are due mainly to decreased blood production. There are two etiologic factors; namely, the intrinsic from the patient's tissues and extrinsic involving the diet. The macrocytic characteristic is seen in pernicious anemia, sprue, pellagra, occasionally in pregnancy, diseases of removal of part of the gastrointestinal tract, hepatic disease and hypothyroidism. Vitamins have some effect not only on the production and maturation of blood cells but, according to results of a recent investigation, on the activity of the cells themselves (Cottingham, E., and Mills, C. A.: Influence of Environmental Temperature and Vitamin Deficiency on Phagocytic Functions, *J. Immunol.* **47**:493-502 [Dec.] 1943).

Conclusions from clinical trial based on subjective symptoms may be erroneous; but in these cases prompt objective improvement in the abnormalities of the skin makes the therapeutic tests more significant.

Mild and subclinical nutritional deficiencies occur in a high percentage of the American population. A deficiency may be caused by any abnormal condition which (1) increases the need of the nutritional factor, i. e., fever; (2) interferes with the absorption or utilization of it; (3) causes its elimination too rapidly, in addition to (4) subnormal intake. Dietary fads and even many diets prescribed by physicians may result in persons' receiving too little of the necessary nutritive essentials.

AMERICAN LEISHMANIASIS

REPORT OF AN AUTOCHTHONOUS CASE

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American leishmaniasis has received scant attention in the literature of the United States, most of the reports having originated from South America, particularly Brazil. While up to 1943 approximately 30 cases of cutaneous leishmaniasis (oriental sore) had been reported from the United States and Canada (1), none of which (with 1 possible exception [1c]) were autochthonous, only 3 cases of American, or mucocutaneous, leishmaniasis had been recorded as occurring in the United States, 1 of which was presumably autochthonous.

McEwen [2] in 1914 published the first case, and, although he called the disease oriental sore, he was undoubtedly dealing with American leishmaniasis. The patient acquired the lesion while traveling in South America. In contradistinction to cutaneous leishmaniasis, the lesion proved resistant to therapy. Furthermore, differentiation between oriental sore and American leishmaniasis had not as yet been made.

Wile,[3] during a discussion in 1942, mentioned that he had recently seen a patient with American leishmaniasis which was contracted in Brazil. No further details were given.

Recently Benedek [4] reported in an English journal a case from Chicago, which he considered to be the first autochthonous case of American leishmaniasis in the United States. However, there is some doubt as to the correctness of this idea. The patient had spent four years in Poland fifteen years prior to the development of mucocutaneous lesions of the nose. Fox,[5] in discussing this case, declared that if the disease was really American leishmaniasis the patient had apparently contracted it in Poland.

The excellent contributions of Howard Fox [6] to American literature on mucocutaneous leishmaniasis were based on studies and observations made during trips to South America and should be consulted by any one interested in the disease.

American leishmaniasis is endemic in South America (except Chile), Central America and the state of Yucatan, Mexico. Many local names have accordingly been given to this disease. *Espundia* and *uta* are names frequently encountered in the textbooks; however, it is the consensus that these are merely local terms for mucocutaneous leishmaniasis.

The disease usually begins as an erythematous, maculopapular or vesicular lesion on an exposed part of the body. This lesion frequently follows an insect bite or slight traumatism. Later a nodule forms, which, as a rule, undergoes ulceration. The ulcers may be few or, rarely, numerous. Generally there are several. The ulcers are round or oval, have a slightly raised firm border and may or may not be crusted. The granulating base is bathed with a moderate amount of secretion. Verrucous and papillomatous forms have been described. When healing occurs, a conspicuous pliable depigmented scar remains. The ulcers heal spontaneously, some within seven or eight months and others lasting for two or three years. This period has been designated as constituting the primary stage, and the lesions have been referred to as chancres.

In 10 to 20 per cent of the cases, after a period ranging from eight or nine months to fifteen years, the mucous membrane of the nose and/or throat is involved. This period is known as the tertiary stage. When, as occasionally happens, the chancres and oral lesions occur in rapid

1. (*a*) Dwork, K. G.: Cutaneous Leishmaniasis (Oriental Sore) in the United States and Canada, Arch. Dermat. & Syph. **45**:676 (April) 1942. (*b*) Silverberg, M. G., and Henschel, E. J.: Oriental Sore in the United States, ibid. **46**:705 (Nov.) 1942. (*c*) Gelber, A.: Oriental Sore Possibly Contracted in the United States, ibid. **46**:739 (Nov.) 1942.

2. McEwen, E. L.: Oriental Sore in the Americas with Report of a Case, J. Cutan. Dis. **32**:275, 1914.

3. Wile, U. J., in discussion on Ebert, M. H.: A Case for Diagnosis, Arch. Dermat. & Syph. **46**:606 (Oct.) 1942.

4. Benedek, T.: American Leishmaniasis, J. Trop. Med. **43**:147 (June 1); 164 (June 15) 1940.

5. Fox, H., in discussion on Benedek, T.: American Leishmaniasis, Arch. Dermat. & Syph. **43**:1093 (June) 1941.

6. Fox, H.: (*a*) American Leishmaniasis, Arch. Dermat. & Syph. **23**:480 (March) 1931; (*b*) American Leishmaniasis, ibid. **30**:241 (Aug.) 1934.

sequence, the latter are regarded as secondary lesions.[7]

The nose, particularly the nasal septum, is most frequently involved; the pharynx and larynx are less often affected. Rarely, the mucous membranes of the esophagus, cheeks and tongue are attacked. According to Fox,[6] the disease begins with congestion, followed by infiltration, vegetation and superficial ulceration. Destruction of the cartilage of the nasal septum results in flattening and distortion of the nose. Occasionally a verrucous type is encountered, the lesion of which may resemble rhinophyma, lupus vulgaris or blastomycosis.

When untreated, the lesions of the mucous membrane show almost no tendency to heal. After years of suffering the patient may die from exhaustion and cachexia.

It is generally agreed that the organism causing American leishmaniasis is Leishmania braziliensis, although morphologically it is identical with Leishmania tropica, which is responsible for oriental sore. Some observers, however, hold to the opinion that the organisms are not different and distinct species. Benedek,[4] for example, constantly referred to L. tropica as the causative organism of American leshmaniasis. Agglutination tests carried out by Noguchi[8] apparently showed that the causative organism of American leishmaniasis differed from the organism producing oriental sore. Later investigators have doubted that the experiments were adequately controlled. At present the controversy remains.

The vector responsible for the transmission of the disease is thought to be the sand fly (Phlebotomus). There are over fifty known species of Phlebotomus, of which more than twenty are found in the Americas. Of these, only three have been reported from the United States. Phlebotomus vexator has been collected from along the Potomac River and from Ansley, La.; Phlebotomus diabolicus, from Del Rio, Sonora and Uvalde, Texas, and Phlebotomus texanus from San Antonio, Texas.[9] It is interesting to note that all of these reports save one have come from or near the state of Texas.

7. Weidman, F.: Leishmaniasis Americana, in Blumer, G.: The Practitioners Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1936, vol. 10, p. 289.

8. Noguchi, H.: Action of Certain Biological, Chemical and Physical Agents upon Cultures of Leishmania: Some Observations on Plant and Insect Hemomonads, in International Conference on Health Problems in Tropical America, Boston, United Fruit Company, 1924; cited by Fox.[5]

9. Carpenter, J. M.: Personal communication to the authors.

The micro-organism, L. braziliensis, is found but sparsely in smears and sections, differing thus from L. tropica, which is seen in great numbers in oriental sores. In sections of the skin or mucous membrane the organism is usually found within large mononuclear cells or free in the tissue spaces, although it is occasionally seen within polymorphonuclear leukocytes and endothelial cells. It has also been observed in affected lymph nodes. Benedek[4] claimed to have demonstrated the organism for the first time in the peripheral circulation by means of the cantharis blister method. Moreover, he reproduced mucocutaneous leishmaniasis in guinea pigs by inoculating the contents of the cantharis blister. This would indicate, as some authors have steadfastly maintained, that American leishmaniasis is a systemic infection and that the late mucocutaneous lesions are due to metastasis rather than to direct transfer of the organism. We favor the latter viewpoint.

When present, the organism is rather easily identified in smears and sections as a round or oval body 2 to 4 microns in diameter, containing a round trophonucleus and a smaller round or rodlike kinetonucleus. It is readily grown on N.N.N. medium. When cultured, it assumes a flagellate form. Reproduction is by longitudinal division, although Benedek[4] and Lanteri[10] observed multiplication also by budding.

The histologic picture is not distinctive. Studies show merely a chronic inflammatory reaction with granulation tissue. At times it may resemble the tuberculoid structure of syphilis or tuberculosis.

Antimony and potassium tartrate injected intravenously and stibophen intramuscularly are the common therapeutic agents. Fox mentioned that a French arsenical preparation resembling arsphenamine had given better results in Brazil. Roentgen rays are apparently of some value. Whereas the cutaneous lesions generally respond satisfactorily to treatment, the mucocutaneous lesions frequently resist all therapy.

REPORT OF CASE

M. M., an American-born Mexican boy aged 6 years, was first seen on Oct. 10, 1942. At that time he complained of ulcers on the dorsum of both feet, on the right knee and on the buttocks of approximately seven months' duration. The first lesion appeared on the dorsum of the left foot and was described as an erythematous papule which the parents considered to be an insect bite. This gradually enlarged and ulcerated.

10. Lanteri, G.: Peculiar Reproductive Types of Leishmania Tropica in Case of Furunculus Orientalis, Gior. ital. di dermat. e sif. **69**:925, 1928; cited by Benedek.[4]

Four months later a similar papule appeared on the dorsum of the right foot, followed shortly by a lesion on the extensor surface of the right knee and one on the right buttock. These, in turn, became ulcerated and crusted. The patient had few subjective symptoms.

The boy had been born on a ranch near Alice, Texas, and had never traveled more than 60 miles (96.5 kilometers) from his birthplace. Otherwise, the past history was of no importance.

Family History.—The father and mother, both of whom were living and well, had been born in the United States. The patient had three brothers and three sisters, who, likewise, were well and free from cutaneous disease. None of the family had ever visited Mexico.

Physical Examination.—Examination in October 1942 revealed a round ulcer on the dorsum of the left foot, approximately 3 cm. in diameter, which was covered with a thick dark crust. Removal of the crust showed a granulating base bathed with a moderate amount of secretion. The border was raised, firm and sloping. There was only slight tenderness to pressure. On the dorsum of the right foot there was a similar but somewhat smaller ulceration. The extensor surface of the right knee and the right buttock each presented a slightly raised dry crusted lesion of about 1 cm. in diameter. Routine physical examination gave essentially negative results except for a generalized lymphadenopathy.

Laboratory Examination.—The Wassermann and Kahn reactions of the blood serum were negative. Examination of the blood showed: hemoglobin content, 86 per cent; color index, 1.04; erythrocytes, 4,180,000; leukocytes, 8,350; polymorphonuclear leukocytes, 37 per cent, of which 34 per cent were mature and 3 per cent stab cells; lymphocytes, 56 per cent; monocytes, 2 per cent; eosinophilic leukocytes, 4 per cent, and basophilic leukocytes, 1 per cent. The urine was normal on examination.

Smears of the exudate taken from several ulcers and stained with Gram's stain showed no leishmaniasis. Cultures of the exudate made on both Sabouraud's and N.N.N. mediums were negative.

Roentgenologic examination of the chest showed no abnormality.

Microscopic Examination.—The first histologic examination of tissue removed from the large ulcer revealed only a nonspecific chronic granuloma. Later, the second specimen for biopsy was taken from the smaller ulcer on the dorsum of the right foot and stained with hematoxylin and eosin (fig. 1). As before, the microscopic picture was that of chronic granulation tissue, the cellular infiltrate consisting mainly of macrophages, plasma cells and lymphocytes, with a few eosinophils. In addition, however, there were many small, round, clear bodies containing a prominent dark-staining round macronucleus and a smaller rod-shaped micronucleus, which was not so easily demonstrated (fig. 2). These bodies were found within large mononuclear cells, vascular endothelial cells and the lumens of small lymphatic vessels and lying free in the tissue spaces.

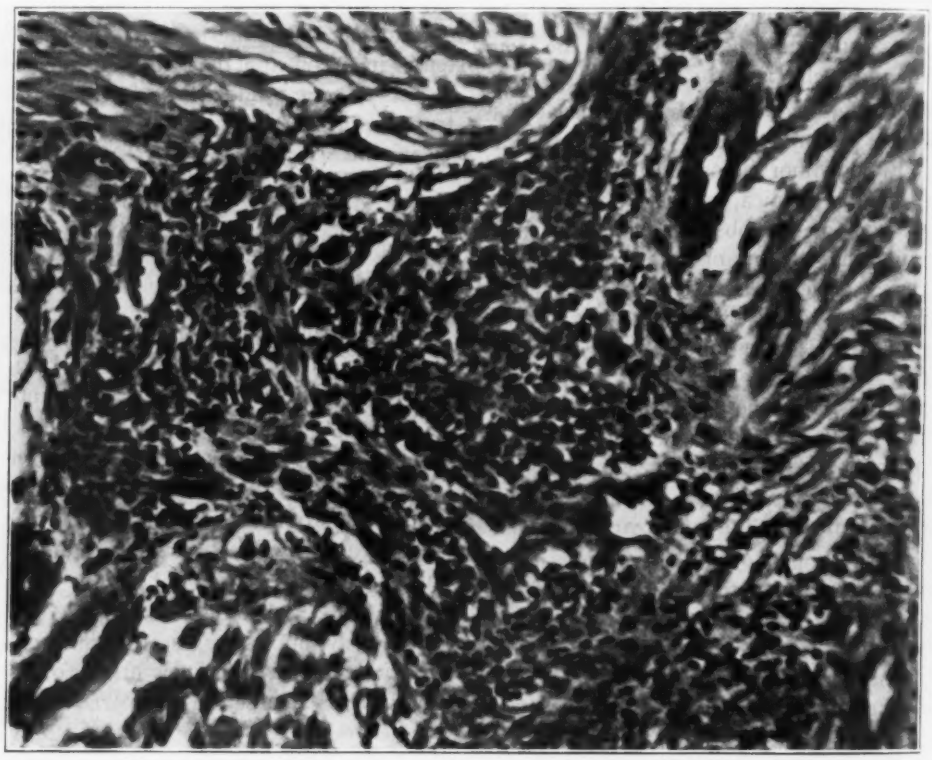

Fig. 1.—Low power photomicrograph of a section from the ulcer on the right foot. Hematoxylin and eosin stain.

Course.—From January 1943, when the diagnosis of American leishmaniasis was made, until July 1943 the patient was lost from observation. Examination on July 4, 1943 revealed the cutaneous ulcerations to be entirely healed with the exception of the large lesion on the dorsum of the left foot. This lesion had almost

disappeared and was considered not worthy of photographing. The sites of the healed ulcers were represented by conspicuous, slightly erythematous, atrophic-looking scars.

The results of a general physical examination, including examination of the mucous membrane of the nose and throat, were again normal except for the persistence of a rather pronounced generalized lymphadenopathy.

The boy's parents attributed his "cure" to the local use of herbs.

The patient was not seen again until May 28, 1944. The skin at this time was clear except for depigmented atrophic scars at the sites of the former lesions. The generalized lymphadenopathy remained but was not so conspicuous as before. Careful examination of the mucous membranes revealed a superficial ulceration, several millimeters in diameter, on both sides of the anterior portion of the nasal septum. There were no subjective symptoms.

Smears and cultures of the serum obtained from a cantharis blister were negative for leishmanias.

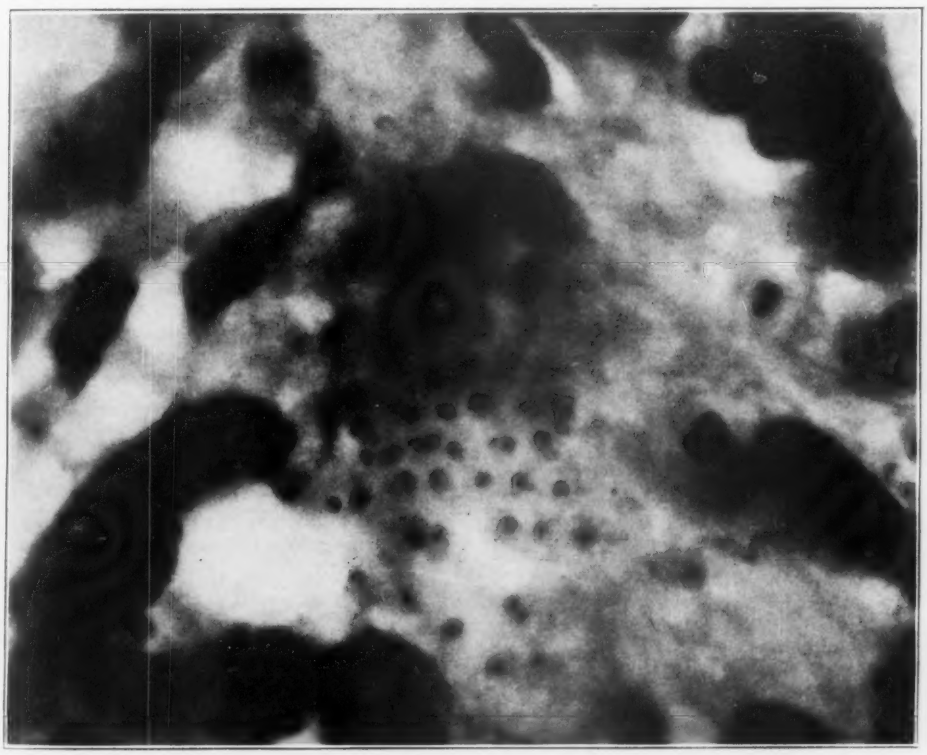

Fig. 2.—High power photomicrograph of a section from the ulcer on the right foot, showing L. braziliensis. Hematoxylin and eosin stain.

COMMENT

Although regional lymphadenopathy in American leishmaniasis has frequently been mentioned in the literature, we found no reports of generalized lymphadenopathy such as was present in our case. The enlargement was striking even from a distance. This was still present almost a year later, although not to the same degree.

Unfortunately, we were unable to demonstrate the organism in smears or cultures, either from the cutaneous lesions or from the peripheral circulation, as Benedek claimed to have done. Perhaps we should have succeeded had the patient been available for more intensive and repeated studies.

We have little doubt that the ulceration of the nasal septum represents the beginning of the tertiary stage of the disease. The appearance and location of the lesion is typical for American leishmaniasis.

It is our opinion that the apparent rarity of the disease in the United States, with only 1 previously identified case, is probably not genuine. If the disease is kept in mind and a diligent persistent search made for the organisms, it is conceivable that many more cases will be discovered, especially in Texas and the Southwestern states bordering on Mexico. Furthermore, it is quite probable that the distribution of the supposed vector, a phlebotomus, is more general than has been reported, as there has apparently been no concerted effort to collect sand flies.[9] To date only three species have been identified from the United States. McEwen as early as

1914 expressed the belief that oriental sore (meaning American leishmaniasis) would probably become endemic in certain sections of the southern states. Today, with numerous military and civilian personnel returning from the endemic areas, we are more than ever inclined to expect the fulfilment of his prediction.

SUMMARY

An autochthonous case of American leishmaniasis with involvement of the lower extremities and nasal septum was encountered in the state of Texas. Three species of the supposed vector, Phlebotomus, have been identified in the United States, all of which are found within or near Texas. It should be remembered that the apparent rarity of the disease in the United States is probably not real. The return of military and civilian personnel from endemic centers is further reason for keeping American leishmaniasis in mind.

Dr. S. W. Becker and Dr. Howard Fox examined the histologic sections, and Dr. S. W. Becker made helpful suggestions regarding the manuscript.

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KAPOSI'S VARICELLIFORM ERUPTION

EXTENSIVE HERPES SIMPLEX AS A COMPLICATION OF ECZEMA

FRANCIS W. LYNCH, M.D.

WITH AN ADDENDUM BY C. A. EVANS, M.D.; VERNON S. BOLIN, B.S., AND RICHARD J. STEVES, M.D.

ST. PAUL

By a series of observations some months ago I was led to the conclusion that the virus of herpes simplex when implanted on diseased skin may result in an eruption of greater severity and extent than the usual group of herpetic vesicles. My attention was first directed to this subject by observation of the eruption the course of which is here described.

CASE 1.—M. L., 2½ years of age, had had atopic eczema for many months, present in a mild form in each cubital area as a papular eruption with occasional exudative manifestations. The course of the eruption changed suddenly, with no evident relation to environmental or dietary changes, when one arm suddenly presented increasing redness, swelling and a papular outbreak. The lesions soon became discrete tense vesicles of a size and tenseness greater than are usually observed in eczematous eruptions. Associated with the development of fever and general toxemia, the eruption extended over the eczematous area and about 1 cm. beyond on the previously normal skin. The area involved was approximately 5 cm. in diameter. After four or five days the vesicles dried in situ and redness and swelling gradually disappeared, leaving the eczema about as before the incident.

In this case the diagnosis of herpes simplex was suggested by a history of exposure to the virus. For about three days before the onset of the child's illness the father had suffered from herpes simplex of an eyelid accompanied by herpetic conjunctivitis. (Smears from the conjunctivas contained no eosinophilic leukocytes or pyogenic bacteria.) At the same time the mother suffered from several aphthous ulcers of the mouth. With this evidence of probable exposure to the herpetic virus a diagnosis of herpes simplex was made, though this diagnosis seems not to be commonly considered in cases of febrile erythematous and vesicular exacerbations of eczematous eruptions.

Within a short time 3 other persons were observed during periods of more severe febrile exacerbations of their eczematous eruptions. There was striking resemblance of their cases to the preceding case, and a similar diagnosis was made in each instance.

CASE 2.—Mrs. T. H., aged 20 years, had had perennial eczema on the arms and hands for seven years and seasonal rhinitis due to sensitivity to ragweed pollen. The eruption extended to the face and neck during the pollen season of 1943 but was greatly improved by October 1. On October 20 she complained of suddenly increased redness and swelling of the face, and when seen on October 22 she presented an extensive eruption of tense vesicles accompanied with submental adenopathy. The eruption became more severe requiring her admission to the hospital on October 24, when the temperature was 102.4 F.; it was 101 F. on the following day. The eruption improved promptly, the temperature becoming normal by October 27, and the patient left the hospital October 29. On her admission to the hospital the white blood cell count was 7,000 per cubic millimeter.

Labial herpes simplex preceded by two days the sudden change in this patient's eruption.

CASE 3.—I first saw R. J., a 10 months old child, on Oct. 26, 1943, when there were scaling and redness of the face with some areas of exudation. The hands were red, swollen, crusted and fissured. Scaling papular plaques were present on the thighs and knees. The eczematous eruption had been present for eight months. The mother was advised to apply compresses moistened with a dilute solution of copper and zinc sulfates and was given a phenolized paste of zinc oxide for the areas where exudation was absent. On October 28 the eruption became much worse and the rectal temperature was 104 F. On October 29 the temperature was 104.5 F. and there were increased redness and swelling associated with numerous tense vesicles on the right cheek, the eyelids and the right hand. Axillary adenopathy was present. Use of the wet dressings was continued. The temperature was 102 F. on October 31 and 101 F. on November 1, when the eruption was greatly improved but had extended at its periphery. Most of the vesicles had ruptured, leaving bright red moist bases. By November 5, ten days after the onset, the eroded areas were healing steadily, though redness and slight swelling were still present.

The mother of this child had had labial herpes simplex for two days before the child's eruption appeared. During the early course of the eruption another physician prescribed oral use of sulfathiazole, which failed to exert a noticeable influence.

From the Division of Dermatology, University of Minnesota, Dr. H. E. Michelson, Director.

Read before the Section on Dermatology and Syphilology at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 14, 1944.

CASE 4.—Mrs. C. P. K., aged 54 years, had had generalized neurodermatitis for several months, and the eruption had been improving slowly and steadily in the hospital for four weeks. Numerous bright red discrete papules appeared suddenly on the face on April 18 and changed to small tense vesicles, a few of which were umbilicated by April 20 (fig. 1). Biopsy was performed on April 21 and fluid removed for animal inoculation. On April 22 each vesicle was crusted and the redness and swelling had disappeared. The temperature was 99.6 F. on April 20 and 100.4 F. on April 21. The white blood cell count was 8,900 on April 21. This patient knew of no exposure to vaccinia or herpes simplex. A microscopic section of cutaneous tissue showed a unilocular vesicle resulting from epithelial degeneration and separation of the epidermis from the cutis (fig. 2). There was evidence of ballooning degeneration and nuclear degeneration. The cellular infiltration extended deeply in the cutis, which was edematous and slightly infiltrated by lymphocytes, probably owing more to the underlying eczema than to the acute complication. The pathologic process corresponded to previous descriptions of severe herpes simplex.[1]

Fig. 1 (case 4).—An extensive vesicular eruption was superimposed on a chronic eczematous background. Umbilicated vesicles are visible on and near the ear and near the eye; other tense vesicles may also be seen, but the majority of the vesicles had ruptured.

The presence of herpetic virus was demonstrated by experimental studies which will be discussed later.[2] In none of these 4 cases was there a history of recent exposure to vaccinia. The 2 children had not been vaccinated. Each of the 2 adults had been successfully vaccinated only once in childhood. These cases were discussed in a brief report before the Ramsey County Medical Society, on April 24, 1944.

In each case the acute herpetic vesicular eruption could have been confused with an acute exacerbation of the eczema or a secondary pyogenic infection. Eczematous exacerbation was ruled out by the absence of a precipitating factor, involvement of only part of the preexisting eruption, presence of fever and toxemia and prompt recovery to the earlier state of the eczema. Pyogenic infection was unlikely in the first case because the eruption improved promptly and steadily without treatment by antiseptics. In the third case there was a failure to respond to oral administration of sulfathiazole.

After a discussion of these cases with other dermatologists it became evident that "herpetization" of eczema has not been commonly recognized. A number of textbooks were then reviewed in an unsuccessful attempt to find references to such eruptions in discussions of eczema or herpes simplex, a fact which suggested that their counterparts must have been regarded previously in some other light. An unrelated condition was discussed in the volumes edited by Darier with brief reference to "vacciniform herpes (Fournier)," an eruption resembling perianal pyoderma.[3] The term "herpetoid eczema" has been used by Sutton and Sutton but only with reference to nummular eczema.

The only personal clinical experiences with conditions comparable with those of the 4 cases herein described were with eczema vaccinatum. This subject was thoroughly reviewed by Tedder,[4] who reported several such cases and described the usual clinical course. After vaccination in the presence of eczema or some other itching eruption there follow redness and swelling and then occurs an outbreak of vesicles which become purulent and umbilicated. Crops of vesicles continue to appear for several days or a week and then become crusted, finally healing with pigmentation and development of pitted scars. This eruption is accompanied with painful swollen lymph nodes, general malaise and high fever, death occurring when the disease is severe.

There seems to be justification for Tedder's conclusion that eczema vaccinatum in most instances represents exogenous inoculation with

1. Schonfeld, W.: Herpes Simplex, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1928, vol. 7, pt. 1, p. 83.

2. Dr. Charles A. Evans, of the department of bacteriology, made the experimental studies which resulted in identification of the herpetic virus in this case.

3. Darier, J., and others: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, vol. 8, p. 288.

4. Tedder, J. W.: Eczema Vaccinatum, Arch. Dermat. & Syph. **34**:1008 (Dec.) 1936.

the vaccinal virus on eczematous skin, but it is less certain that Kaposi's varicelliform eruption and pustulosis vacciniformis acuta are synonyms of eczema vaccinatum. Certainly in some cases the latter terms have been used to describe eczema vaccinatum when there was no history of vaccination, but the clinical features of the three diseases are not always identical. If eczema vaccinatum and Kaposi's varicelliform eruption are synonymous, it is difficult to understand why

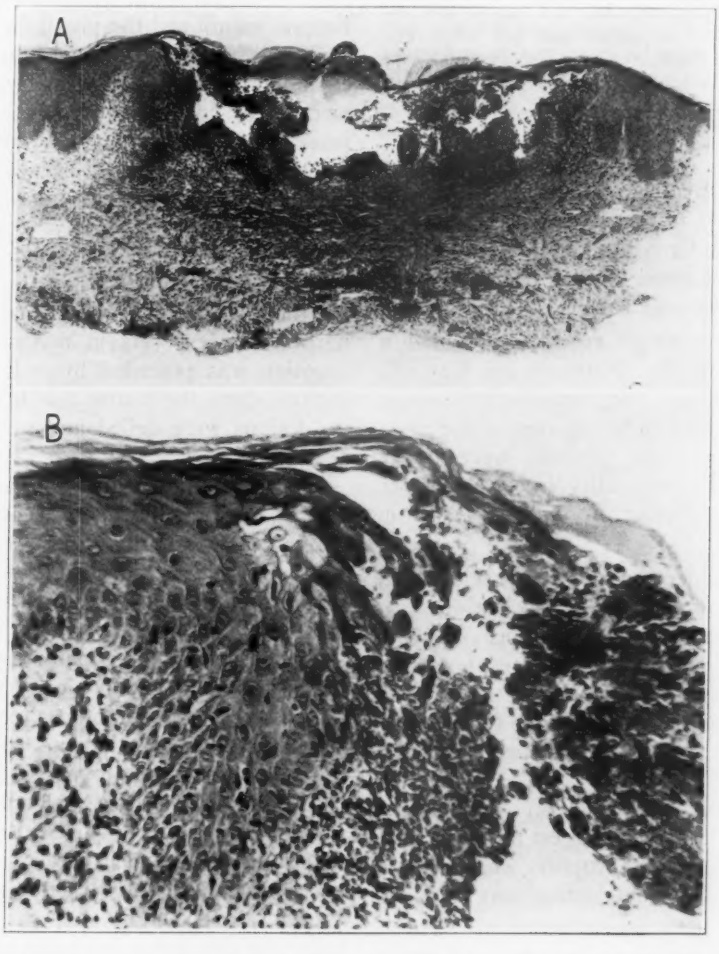

Fig. 2.—Photomicrograph of a section of tissue from a vesicle (case 4). *A*, a unilocular vesicle with epithelial degeneration and underlying cellular infiltration; *B*, degenerative changes in the epithelial cells characteristic of viral diseases.

experienced dermatologists have disagreed so frequently as to the nature of the latter disease. In some cases it has been assumed that the vaccinal virus was borne to the skin through the blood; in others it was thought to have been spread by unrecognized external contact. There is dissimilarity with reference to the history of previous, concurrent or subsequent vaccination. In many reports the lesions are said to have resembled several diseases rather than one—that is, variola, varicella, vaccinia, zoster with generalization and erythema multiforme. In a number of instances pyogenic organisms appear to have caused similar eruptions, resulting in an epidemic in the series reported by McLachlan and Gillespie.[5] Having observed the superimposition of herpes simplex on eczematous eruptions, I believe that the same sequence occurred in certain cases previously reported under the titles proposed by Kaposi,[6] Juliusberg[7] and others.

Kaposi's original contribution provided a clear and concise description which may profitably be repeated here. He observed at least 10 children

5. McLachlan, A. D., and Gillespie, M.: Kaposi's Varicelliform Eruption: Epidemic of Sixteen Cases, Brit. J. Dermat. **48**:337, 1936.

6. Kaposi, M.: Pathology and Treatment of Diseases of the Skin, ed. 4, translated by J. C. Johnston, New York, William Wood and Company, 1895, p. 346.

7. Juliusberg, F.: Ueber Pustulosis acuta varioliformis, Arch. f. Dermat. u. Syph. **46**:21, 1898.

with an acute outbreak of numerous vesicles, partly scattered and partly arranged in groups.

> The vesicles are as large as a lentil, filled with clear serum, and the majority are umbilicated. They look like varicella vesicles but undoubtedly do not belong to this class. The integument which has been attacked in this manner now appears still more swollen, even tense. The little patients have high fever (40° C. or more) and are very restless. The vesicles develop very acutely (sometimes over night), in large numbers, and often continue to appear, in successive crops, for three or four days or even a week. Those which appeared first undergo desiccation, rupture, and expose the corium, or they become encrusted and fall off. The largest number of these varicella-like vesicles are found on already eczematous skin, but smaller groups appear upon the previously intact skin of the neighborhood, upon the forehead, ear, neck, and even the shoulders and arms.

Death followed involvement of the nervous system in at least 1 of the 10 cases. The presence of swollen, tender regional lymph nodes was not mentioned by Kaposi but has been described by numerous subsequent writers.

Barton and Brunsting [8] recently provided a thorough review of the literature on Kaposi's varicelliform eruption. They reported that atopic dermatitis was present in 80 per cent of the cases and in 75 per cent the patients were under 4 years of age. The mortality rate was 25 per cent, being much higher in children than in adults.

Certain of the older reports were reviewed in a search for mention of herpetic associations. In none is there a clear history of presence of herpes simplex in the patient or his associates, but some of the descriptions have resemblance to the cases I have reported here. It is possible that Juliusberg's case is an example of herpetic inoculation on an eczematous background.[7] The mother of the patient had on one eyelid an eruption the nature and course of which suggest the possibility of herpes simplex. (The eruption was not seen by Juliusberg, and the description was provided by another physician; all dermatologists know how frequently physicians fail to recognize herpes of the eyelids). She had previously been vaccinated on two occasions; hence it is unlikely that an accidental inoculation with vaccinal virus would have resulted in primary vaccinia. If the mother's eruption was herpetic, that of the child may have been also. In describing a herpetic eruption on an eyelid Andervont and Friedenwald [9] pointed out that had the herpetic virus not been demonstrated the eruption "would have been regarded as a typical example of accidental infection with vaccine virus." The photograph of their patient shows an eruption the description of which would match that of the mother of Juliusberg's patient.

In the case of the child described by Freund [10] there had been no previous vaccination and after the disappearance of the vesicular eruption it was possible to inoculate successfully with vaccinia. Freund mentioned the possibility of eczema vaccinatum's being confused with herpes simplex but excluded the latter diagnosis because the herpetic virus was not demonstrated and delling was present, though he pointed out that delling is sometimes observed in herpes simplex. In a number of other reports subsequent vaccination was successful.

Goeckerman and Wilhelm [11] described an eruption much like that of Mrs. T. H. (case 2), but there was no note of apparent relationship to herpes simplex. As in my case, the vesicular eruption was preceded by redness and swelling for two days, the course was brief, only a few of the lesions were delled and pustulation was not present.

Under the title "Kaposi's Varicelliform Eruption" Corson and Ludy [12] reported 3 cases; in the first the possibility of herpes may be suspected because of the presence of coryza, limitation of the eruption to one cheek and absence of scarring.

Since Kaposi [6] originally suggested "eczema herpetiforme" as the name for the disease which has since been spoken of as a "varicelliform eruption," it is ironic that its cause should have remained obscure for forty-five years while it was confused with vaccinia and other infectious diseases. However, in 1941 Seidenberg [13] described experimental studies in 2 cases which he reported under the title of "Pustulosis Vacciniformis Acuta." In the study of the first case he successfully inoculated the cornea of a rabbit, producing an inflammatory reaction from which subsequent

8. Barton, R. L., and Brunsting, L. A.: Kaposi's Varicelliform Eruption, Proc. Staff Meet., Mayo Clin. **18**:199, 1943.

This publication is an abbreviated report. The more complete paper is to be published in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY. The authors kindly allowed examination of the unpublished manuscript and use of lantern slides illustrating their cases.

9. Andervont, H. B., and Friedenwald, J. S.: A Case of Vacciniform Blepharitis Due to an Atypical Herpes Virus, Bull. Johns Hopkins Hosp. **42**:1, 1928.

10. Freund, H.: Zur Aetiologie der Pustolosis vacciniformis acuta (Kaposi-Juliusberg), Dermat. Wchnschr. **98**:52, 1934.

11. Goeckerman, W. H., and Wilhelm, L. F.: Kaposi's Varicelliform Eruption, Arch. Dermat. & Syph. **32**:59 (July) 1935.

12. Corson, E. F., and Ludy, J. B.: Kaposi's Varicelliform Eruption: Report of Three Cases, Am. J. Dis. Child. **50**:1476 (Dec.) 1935.

13. Scidenberg, S.: Zur Aetiologie der Pustulosis vacciformis acuta, Schweiz. Ztschr. f. Path. u. Bakt. **4**:398, 1941.

transfers were successful. In the study of the second case a series of rabbits were inoculated and subsequently shown to be immune to inoculation with the virus of vaccinia. Seidenberg concluded that the disease is not etiologically connected with vaccinia and is probably a manifestation of herpetic infection in a person with exudative diathesis.

Ronchese [14] recently reported a case as eczema vaccinatum. He mentioned Seidenberg's experimental studies but questioned whether Kaposi's varicelliform eruption would be so severe and so infrequent and would fail to recur if it were caused by the virus of herpes simplex. He concluded that "a relation of dermatitis vaccinica to herpes simplex is most unlikely."

On the basis of recent observation of 2 cases Barton and Brunsting [8] came to the same conclusion as I—that there is little support for a theory that such eruptions are caused by the virus of vaccinia but that there is more evidence to support the opinion that Kaposi's varicelliform eruption usually results from an eczematous person's reactions to the virus of herpes simplex. Both patients were adults having atopic dermatitis; each eruption was preceded by ordinary herpes simplex of the lip or chin. In 1 case there were signs and symptoms of involvement of the central nervous system; the patient was extremely ill and ultimately presented a generalized eruption. Virus from 1 patient was transferred to a rabbit, in which it produced herpetic keratitis, and then to a mouse, in which encephalitis developed. Serum of this mouse afforded effective protection to other mice later inoculated with lethal doses of herpetic virus.

In recent weeks there have been two additional reports. Wenner [15] described extensive eruptions in 3 infants with Kaposi's varicelliform eruption. From the lesions he obtained viruses which were identified as herpetic. Blattner, Heys and Harrison [16] have prepared a preliminary report of studies with a virus obtained from a patient recently observed by Dr. Clinton Lane.[17] This virus was inoculated on chorioallantoic membranes of chick embryos, where it produced numerous small opaque pocklike lesions, from which the virus was transferred to mice and rabbits, in which it produced encephalitis.

Vesicular contents from my fourth patient (Mrs. C. P. K.) were inoculated on the scarified corneas of 2 rabbits. (The corneas of the opposite eyes were scarified but not inoculated; no keratitis developed there.) Typical herpetic keratitis appeared within forty-eight hours. After five days 1 rabbit was killed and the eye sectioned and stained, allowing demonstration of the eosinophilic intranuclear inclusion bodies of herpes simplex. The second rabbit acquired encephalitis with subsequent paralysis of the opposite lower extremity. After three weeks the second rabbit was killed and the blood used in neutralization experiments which determined the presence of antibodies against herpetic virus.

Each of 6 mice was inoculated with 0.05 cc. of vesicular fluid, death resulting in seven to fifteen days. From their brains was obtained virus for inoculation into other mice. Immunologic and neutralization studies are still being carried out.

COMMENT

There remains little doubt that Kaposi's varicelliform eruption can result from inoculation with the virus of herpes simplex. The experimental studies reported by several previous authors and the contents of the present report are sufficient evidence that the herpetic virus can produce such an eruption as a complication of eczema and certain other diseases. This eruption varies in extent, but in the more severe forms it cannot be distinguished from the disorders described by Kaposi, Juliusberg and other observers under a variety of titles. It remains a question whether all previous cases should be regarded as examples of herpetic infection. I have listed a few instances in which the evidence favors that interpretation of the case. In other instances these eruptions may have represented eczema vaccinatum, though proof of the true cause was not demonstrable by a history of exposure to the virus of vaccinia. In still other cases the tense vesicles may have resulted from infection with pyogenic organisms. Perhaps further studies will demonstrate additional causes of such varicelliform eruptions.

It may be difficult to differentiate the several varicelliform eruptions. Tenseness and umbilication of the vesicles make it less likely that one is dealing with pyogenic infections.[5] Smears and cultures are inconclusive because pyogenic organisms may complicate viral infections. Biopsy can be used to differentiate pyogenic from viral eruptions, but herpetic and vaccinal eruptions cannot be distinguished with certainty. In a given case failure of an eruption to respond to therapy with sulfonamide compounds must be regarded as evidence suggestive of a viral cause.

14. Ronchese, F.: Dermatitis Vaccinica, Arch. Dermat. & Syph. **47**:613 (May) 1943.

15. Wenner, H. A.: Complications of Infantile Eczema Caused by the Virus of Herpes Simplex, Am. J. Dis. Child. **67**:247 (April) 1944.

16. Blattner, R. J.; Heys, F. M., and Harrison, M.: A Filterable Virus Isolated from a Case of Kaposi's Varicelliform Eruption, Science **99**:432, 1944.

17. Lane, C. W.: Personal communication to the author.

Failures have been observed with sulfanilamide by Goeckerman and Wilhelm and with sulfathiazole by Barton and Brunsting (2 cases) and by me in case 3 of the present report. Stephen Epstein [18] administered both sulfadiazine and sulfathiazole to 2 infants and thought that the results suggested only that the drugs aided in control of the secondary infection. Connor and Gonce [19] reported inconclusive results.

Vaccinal and herpetic eruptions can probably be distinguished clinically in the majority of instances (experimental studies can be conclusive). The vesicles of eczema vaccinatum are as a rule fewer, larger and tenser, and more of them are pustular or umbilicated. The eruption and the general illness are longer than in cases of eczema herpeticum. The vesicles of eczema herpeticum are moderately tense; they tend to be grouped or to coalesce, and the majority do not develop umbilication. It is possible that involvement of the central nervous system is more frequently observed with herpetic infection, but both viruses are neurotropic to some extent. The lesions tend to rupture; if discrete, they may crust and heal; if more numerous, they coalesce as bright red erosions which heal by epithelization. In both diseases the progress of the viral disease is modified to some extent by the site, extent and severity of the previous eczema or other dermatosis.

Since so few cases have yet been proved to be examples of herpetic complication of eczema, it is impossible to estimate the prognosis or to describe the course in greater detail. Milder eruptions have been observed (case 1) and will perhaps be found to be more numerous than the severe eruptions.

SUMMARY

Infectious complications of eczema may be pyogenic or viral. "Kaposi's varicelliform eruption," "Juliusberg's pustulosis vacciniformis acuta," "eczema vaccinatum," "impetiginized eczema" and other terms have been applied to these complications. By some writers the first three terms have been regarded as synonymous, but this opinion seems to be an error. Eczema vaccinatum is a distinct entity caused by the virus of vaccinia. Kaposi's and Juliusberg's terms probably apply to a group of disorders the clinical appearance of which is similar.

Of these patients at least some and probably many have eruptions resulting from implantation of the virus of herpes simplex on previously disturbed skin. The background is usually that of eczema, but in some instances other dermatoses precede the acute eruption. The degree of severity may depend on the virulence of the virus, the susceptibility of the host and the nature and extent of the preceding eruption. In most instances it should be possible to recognize this condition by clinical observation. In describing 4 examples of herpetic complication of eczema I pointed out that the disease need not be severe (case 1).

The results of experimental studies confirm the data published by certain other workers.

In this report are described 2 cases in which the eruption was diffuse at the onset and the source of the infection was a parent with herpes simplex (cases 1 and 3). In case 4 the source of the infection was not determined, but the nature of the eruption was established by clinical observation, microcopic study of a vesicle and experimental studies with the virus obtained from vesicular contents. Most previously reported cases resemble case 4 in that the source of infection was not recognized because the eruption was diffuse and extensive when first seen. As in my case 2, Barton and Brunsting recognized labial herpes simplex in their 2 patients.

"Kaposi's varicelliform eruption" does not seem to be a suitable name for an eruption caused by the herpetic virus. There is no need for the name to point out the slight resemblance to varicella; no one believes the virus of varicella to be concerned in the development of these eruptions. Kaposi originally suggested that the eruption be spoken of as "eczema herpetiforme," but the eruption not only resembles herpes simplex—it *is* that disease in an extensive form. In cases in which the herpetic virus is incriminated and following the usage established by application of the term "eczema vaccinatum," Kaposi's varicelliform eruption could well be regarded as "eczema herpeticum" or spoken of as extensive herpes simplex complicating eczema (or other dermatoses).

ADDENDUM: EXPERIMENTAL DATA WITH SUGGESTED THERAPEUTIC APPLICATION [20]

C. A. EVANS, M.D.,[21] VERNON S. BOLIN, B.S.,[21] AND RICHARD J. STEVES, M.D.[22]

The conclusion that the virus of herpes simplex caused the eruption in this case (case 4) is based on the following experimental evidence.

18. Epstein, S.: Personal communication to the author.

19. Connor, A., and Gonce, J. E., Jr.: The Treatment of Kaposi's Varicelliform Eruption with Sulphonamide Drugs, J. Pediat. **24**:335, 1943.

20. Aided by grants from the John and Mary R. Markle Foundation and the Graduate School of the University of Minnesota.

21. From the Department of Bacteriology of the University of Minnesota.

22. From the Division of Dermatology of the University of Minnesota.

Vesicle fluid collected on the third day of illness was inoculated into 5 mice intracranially. Four died on the sixth to eighth days with the appearance of having an encephalitis. Subsequent brain to brain passage resulted in a regularly fatal illness with the usual appearance of herpetic encephalitis in mice. Aerobic and anaerobic cultures proved the brains of infected mice to be bacteriologically sterile. The brain of 1 mouse was subjected to microscopic study. Typical herpetic intranuclear inclusion bodies were found in the nerve cells.

Corneal inoculation of 2 rabbits was performed with the same specimen of vesicle fluid as was used for inoculation of mice. At three days a severe purulent keratoconjunctivitis was present in the inoculated eye of each rabbit. One animal was killed at this time. Sections of the inoculated eye showed that most of the corneal epithelium had sloughed off. Near the limbus, remaining epithelial cells showed granular acidophilic intranuclear inclusions of the sort known to be caused by the virus of herpes simplex. At seven days in the second rabbit a disturbance of equilibrium developed that caused it to move in circles, going toward the side of the inoculated eye. On the eleventh day a paresis of the right hindleg was noted. At twenty days the disturbance of equilibrium and the paresis were still present.

A third rabbit (K 194) was inoculated by corneal scarification with brain from a mouse representing the second passage of the virus in mice. Again the typical keratoconjunctivitis and a moderate disturbance of equilibrium resulted. Serum collected two days and twenty-seven days after inoculation was tested for antibodies to the virus of herpes simplex. Various dilutions of serum were mixed with sufficient virus to equal approximately ten minimal lethal doses in each 0.025 cc. of mixture (HF strain, mouse brain diluted to 10^{-4}). After standing for one hour at room temperature each mixture was injected in a dose of 0.025 cc. intracerebrally into 3 mice. The results, as shown in the table, demonstrated clearly that the animal acquired antibodies to the virus of herpes simplex during the period of the infection.

Neutralization of the Virus of Herpes Simplex (HF Strain)

S indicates that the mouse survived until discarded at two weeks. All tests were made at the same time. Into each of three mice a serum-virus mixture was injected. Each number indicates the day after inoculation that a mouse died.

	Dilution of Serum					
Source of Serum	1:2	1:10	1:20	1:40	1:80	1:160
Rabbit K194 at 2 days.	333	333	334	333	133	334
Rabbit K194 at 27 days	S8S	S87	S59	S87	S55	455
Patient, April 21.....	S8S	S8S	S8S	S8S	355	445
Patient, 74 days later..	S8S	S8S	S86	S8S	556	S77
25 normal human subjects (pooled serum)	S8S	S8S	S8S	S8S	S57	445

It is known that many, if not most, normal adults have antibodies to herpes virus in their blood stream.[23] It was of interest, therefore, to determine whether this patient had such antibodies. Serum collected at the same time vesicle fluid was obtained for isolation of virus (the third day of the eruption) was found to have antibodies in considerable amount. Serum collected seventy-five days later showed no significant difference in antibody titer. A pool of serum from 15 normal persons contained approximately the same amount of antibodies as this patient's serum.

COMMENT

Characteristic infection in rabbits and in mice, the presence of typical inclusion bodies and the development of specific antibodies in an infected rabbit prove that the virus of herpes simplex was present in the vesicles of this patient and presumably caused the eruption. Serum collected from the patient on the third day of the eruption contained antiherpetic antibodies in considerable amount. The titer of these antibodies may have increased during the preceding two days, but there can be little doubt that antibodies were present at the time the eruption began. This is not surprising in view of the known occurrence of ordinary herpetic infections in persons with significant antibody titers in their serum.

It is known that eruptions of the sort commonly called Kaposi's dermatitis may be of a serious nature, and fatal cases have frequently been reported. Whether these severe and sometimes fatal eruptions may be caused by the virus of herpes simplex is not known. If so, there must be a spread of the virus to involve organs other than the skin, a possibility that might reasonably be expected, especially in young children, in view of the ability of this virus to infect many organs and tissues of experimental animals.[24] If true, this fact would be of considerable therapeutic significance. Specific antibodies are capable of interfering with the spread of an established herpetic infection in young mice.[25] Inasmuch as a pool of normal human plasma or serum (see the table) is likely to contain considerable amounts of the specific antibody, the injection of pooled serum or plasma would seem to offer a simple therapeutic measure that might prove to be of real value. It is to be emphasized that such therapy would have a rational basis only in the case of eruptions that might reasonably be considered as caused by the virus of herpes simplex.

ABSTRACT OF DISCUSSION

DR. OLIVER S. ORMSBY, Chicago: Much work has been done by several competent observers, most of whom were concerned chiefly in demonstrating the presence or absence of Guarnieri bodies, connecting the disease etiologically with vaccinia. The majority found

23. Zinnser, H., and Tang, F.: J. Immunol. **17**:343, 1929. Andrews, C. H., and Carmichael, E. A.: Lancet **1**:857, 1930. Brain, R. T.: Brit. J. Exper. Path. **13**: 166, 1937. Gildemeister, E., and Ahlfeld, I.: Zentralbl. f. Bakt. (Abt. I) **139**:325, 1937. Burnet, F. M., and Lush, D.: Lancet **1**:629, 1939.

24. Goodpasture, E. W., and Teague, O.: J. M. Research **44**:121, 1923. Slavin, B., and Berry, G. P.: J. Exper. Med. **78**:321, 1943.

25. Evans, C. A.; Slavin, H. B., and Berry, G. P.: J. Bact. **47**:63, 1944.

no such connection. Some observers have concluded that the disease has a pyogenic cause. The clinical picture of Kaposi's varicella eruption and that of Juliusberg's [7] pustulosis vacciniformis acuta are identical, and it is generally accepted that they represent a single disease. Eczema vaccinatum, so well described and discussed by Tedder,[4] resembles the disease under discussion but can be distinguished clinically, as can also the many cases seen in which a pyodermic or impetigenous infection occurs superimposed on an eczema. I have seen a number of these cases in children in whom the secondary pyoderma was extreme but no constitutional symptoms were present. I have also seen extensive herpes simplex in children with no eczematous background in whom no constitutional symptoms occurred. It must be that the growth of the herpes virus on an eczematous skin produces a much more serious reaction, both local and constitutional, in these cases. In 2 patients with Kaposi's varicella eruption the constitutional symptoms were pronounced, the temperature in 1 going up to 106 F. In 1 of these, a man aged 23, hemolytic staphylococci were found in blood cultures, and sulfathiazole was administered for two days before I saw the patient. His leukocytes were reduced to 2,200. The sulfathiazole had no immediate effect on the disease. He was given a blood transfusion and the administration of sulfathiazole was stopped, and in four days the leukocytes had risen to 7,000 and the disease was under control. The condition cleared in three weeks, a typical atopic dermatitis being left. Shortly afterward, I saw a child with a typical eruption implanted on an old eczema (the patient was 13 months of age). The temperature was 103 F., and the leukocytes numbered 8,900. This patient had been successfully vaccinated. It is interesting to note that Wise and Sulzberger (Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1942, p. 151) editorially suggested the herpes virus as the cause. Dr. Lynch's experimental observations appear conclusive as to the etiologic role of the herpes virus in these cases, and I am sure that future investigators will confirm his conclusions.

Dr. Clinton W. Lane, St. Louis: In the last eighteen months 5 patients with Kaposi's varicelliform eruption have been observed. Their cases had many resemblances to the cases described by Dr. Lynch, but they exhibited a few differences. The patients varied in age from 6 months to 20 years, and all of them had typical atopic dermatitis. The Kaposi varicelliform eruption began suddenly with fever and cervical adenopathy; the adenopathy was pronounced and was one of the striking features of the disease. Within twenty-four to forty-eight hours an eruption appeared on the face and neck, with rapid extension to other areas. The lesions were vesicles and bullae, most of which were umbilicated. Accompanying the eruption was an actual or relative leukopenia. The course was acute and stormy, and all the patients recovered without sequelae. A virus causation was suspected but was proved for only 1 patient, the fifth in the series. The report of the virologic studies has previously been reported in *Science* by Drs. Blattner and Heys, who proved that the virus is closely related to or is a form of herpes simplex virus. This substantiates the opinion of Dr. Lynch that the disease is not a form of eczema vaccinatum. At variance with the experience of Dr. Lynch was the fact that there was no history of antecedent herpes simplex for any of these patients, nor was there a known contact with herpes simplex in a parent, relative or other persons.

In support of the statement that the sulfonamide compounds were useless was their failure to produce improvement in the 3 patients to whom they were administered. In 1 infant sulfathiazole reduced the white blood cell count to a dangerous level, but on withdrawal of the drug the leukocyte count immediately rose.

In an effort to propose a more appropriate name for this disease without denying to Kaposi the credit for the initial recognition, it is suggested that the disease be known as Kaposi's herpetiform eruption.

Commander Marion B. Sulzberger (MC), U.S.N.R.: I believe that in the Year Book of Dermatology and Syphilology for 1942 Dr. Wise and I stated that these varicelliform eruptions were not uncommon in our patients with severe atopic dermatitis and expressed the opinion that the disease might have been due to a generalized or rather widespread external inoculation or hematogenous distribution and fixation of herpes virus in the open and scratched areas abounding in these patients. The splendid work reported by Lynch and by others has now confirmed what was previously a mere assumption.

There are many forms of herpes simplex infection in addition to the classic "cold sore" or "fever blister," which can be recognized by all. There is, for example, the recurrent herpetic paronychia and the recurrent bullous herpes simplex of the finger, which often resembles an eczematous eruption or a fixed bullous drug eruption in their recurrence in fixed areas. These were described by the late Wilhelm Frei. There is the follicular and sycosiform herpes simplex of the bearded area, with minute discrete vesicles and/or crusts, often accompanied by severe itching. There is the zosteriform herpes simplex, simulating herpes zoster in its arrangement along the course of nerves. And there is the herpetic stomatitis with its stormy course. In cases such as these, only the modified Paul experiment or other demonstration of the herpes simplex virus will establish the diagnosis.

The knowledge of these variants, as well as the observation that in some of our patients with atopic dermatitis the varicelliform eruption was preceded either by exposure to vaccinia or by exposure to a "fever blister" led us to the conclusion that some instances of Kaposi's eruption were caused by herpes simplex virus. I think that there are milder forms of Kaposi's varicelliform eruption which are not at all uncommon.

One of the lessons which should be learned from Dr. Lynch's excellent study is that there may be other vesicular diseases, now of unknown cause, which are due to herpes virus. In particular, certain common vesicular eruptions of the hands and feet, now usually called "dyshidrosis" or even "eczema," have many features which to me suggest a recurrent herpetic infection. And the same applies to the condition known as nummular eczema. I wonder whether Dr. Lynch or any of the other workers in this field have made a serious attempt to examine these conditions from that point of view.

I think that the word "eczema" should not be used in describing Kaposi's varicelliform eruption. There are already too many confusions surrounding the term "eczema." Why not call this eruption "disseminated herpes simplex," or call it "Kaposi's form of herpes simplex" if one wants to preserve his name?

Dr. Francis Ellis, Baltimore: Eczema vaccinatum occurs fairly frequently. I saw 3 cases during the past winter. From what I could tell from the pictures Dr. Lynch showed on the screen, the eruptions looked different from those of my patients, the individual

sions of which were larger and umbilication was a more prominent feature. The pictures either were not distinct or apparently were taken after involution had set in. In his microscopic picture one could not identify the virus, as several investigators (Ellis, F. A.: Eczema Vaccinatum: Its Relation to Generalized Vaccinia, *J. A. M. A.* **104**:1891 [May 25] 1935; People, A. W., Murrell, T. W., Fowlkes, R. W.: South. M. J. **35**: 967, 1942, and Combes, F. C., and Behrman, *New York State J. Med.*, **43**:2283, 1943) have been able to do, perhaps because the biopsy specimen was not obtained sufficiently early.

Kaposi's varicelliform eruptions apparently may be caused by several different etiologic factors, namely, vaccinia, streptococcic infection (McLachlan, A. D., and Gillespie, M.: *Brit. J. Dermat.*, **43**:337, 1936), and now the herpes simplex virus. The herpes simplex virus usually does not cause toxemia, fever and a generalized eruption. The microscopic appearances in tissue of the herpetic and vaccinia virus are so different that there should not be any difficulty in differentiating between them. In the human being the herpes simplex virus does not give immunity. I do not know whether it does in the rabbit. The literature shows that vaccinia does not always give immunity. Gordon (*Brit. J. Dermat.* **48**:525, 1936), C. E. Van Rooyen (*Brit. J. Dermat.* **48**:669, 1936) and Brain and Lewis (*Brit. J. Dermat.* **49**:551, 1937), who aided in the investigation of McLachlan's patients, were unable to conclude that their eruptions were due to a virus.

Dr. Lynch should be complimented on emphasizing that Kaposi's varicelliform eruption may be due to some other etiologic agent. Generalized eruptions may be associated with herpes zoster, but the lesions look like varicella and not like Kaposi's varicelliform eruptions.

Dr. M. Ebert, Chicago: I have attempted to demonstrate Guarnieri inclusion bodies in the cytoplasm of the cells in experimental animals and in the lesions of the patient himself, always with failure. I never thought about herpes. I have studied the cases of 3 patients, 2 children and 1 adult, in an attempt to demonstrate vaccinia virus. All were failures. There were no Guarnieri bodies, either in the tissue of the patient or in the experimental animal. And the 2 young children were afterward successfully vaccinated, which means something, I believe, because such a violent reaction to vaccinia virus should produce an immunity for at least some time.

Recently, through the courtesy of Dr. Zinner, I saw a patient with an eruption of this type in the Illinois Research Hospital, a young woman whose condition was much more severe than that of any of those that Dr. Lynch mentioned and more like the ones described by the last speaker. This patient was acutely ill, had a high fever and had crops of lesions that certainly resembled variola. Material was taken from the lesions, and attempts were made to demonstrate elementary bodies. This was impossible, largely, I think, on account of the secondary infection and the fact that the material was taken a little too late. It must be taken at exactly the right time, when the vesicle contents still are clear. Then inoculation on rabbits' eyes was successful, producing violent keratitis, which I ascribed, unfortunately, to secondary infection.

On going over the sections again after I had heard Dr. Lynch's paper, I found that the typical inclusion bodies which are found in the herpes group, (that is, in herpes zoster, in herpes simplex and in chickenpox) were found not only in the rabbit's eye where the material had been transmitted experimentally but in the lesions taken from the skin of the patient himself. So this would limit, I believe, as far as is known now about inclusion bodies, the disease to one of those three.

I disagree with some of the other speakers that a primary herpes infection does not produce a violent illness or high temperature. In his review of the herpes virus about twenty years ago, Doerr, a Swiss investigator, mentioned the fact that in Europe it was not infrequent to see persons with what was called "herpetiform fever," an initial attack of a very violent herpetic eruption associated with high temperature, malaise and headaches in a person who had never before suffered from herpes simplex.

Dr. Francis W. Lynch, St. Paul: Dr. Ormsby pointed out that the general symptoms are more severe and the white blood cell count less elevated than might be expected with the degree of fever and extent of the eruption, respectively. These characteristics are also observed frequently in other diseases caused by viruses (e. g., influenza).

The presence of lymphadenopathy was not recorded by Kaposi, but, as Dr. Lane indicated, it is frequently present and in severe forms of the disease it may be a striking feature. I do not believe that extensive lymphadenopathy or the presence of pustules need be expected in all cases; milder examples of the disease are probably more common than severe ones, and in such cases only tense vesicles may be present, many of them never developing even to the stage of umbilication. As Dr. Ebert pointed out, the first inoculation with the virus of herpes simplex often produces a more severe reaction than does reinoculation. This probably explains to some extent the fact that this disease is more severe in infants and small children, who have probably not previously been exposed to the virus.

As suggested by Dr. Sulzberger, herpes simplex is often more important than a simple "cold sore," and clinical variations are numerous. One variant, "herpetic fever," was mentioned also by Dr. Ebert. It is given extensive discussion by Schonfeld in Jadassohn's "Handbuch."

It is unlikely that biopsy will be frequently applied as a diagnostic procedure in cases of this disease, yet it might be of greater assistance than the remarks of Dr. Ellis suggest. With this aid one can easily distinguish viral infection from ordinary eczema or its pyogenic complications. It is more difficult to distinguish between eczema vaccinatum and herpetic complications of eczema.

Dr. Ebert has been particularly interested in studies with viruses, and his discussion and that of Dr. Sulzberger suggest how difficult are experimental studies in that field. Negative experimental evidence is of little significance. Demonstration of the virus usually requires study of an unruptured vesicle, preferably not over one or two days old. For these reasons it is likely that the diagnosis of herpetic complication of eczema will usually be made on a clinical basis. The pathogenesis seems to be well established, and it is now only necessary for clinicians to become familiar with the disease.

Clinical Notes

SULFAPYRIDINE AS A HEMOSTATIC AGENT

C. Russell Anderson, M.D., Los Angeles

In 1942 Cunningham [1] reported on the use of sulfapyridine as a hemostatic agent. He found that after sulfamethylthiazole powder had been instilled into the operative wound after radical external frontal sinusotomy for osteomyelitis of the frontal bone the usual considerable postoperative oozing was absent. This observation led him to experiments on guinea pigs. Circular wounds were made on the backs of the animals, and five to seven days later the scabs were evulsed so that an open granulating and freely oozing surface remained. Powdered sulfapyridine, sulfanilamide, sulfathiazole, sulfamethylthiazole [2] and talc were sprayed on with a powder blower. The wounds treated with sulfamethylthiazole and sulfapyridine exhibited an immediate tendency to hemostasis, while the wounds treated with the other powders and with talc and untreated control wounds all oozed for from five to ten minutes. The sulfapyridine powder was also found to be bacteriostatic. The results of this experimental work led Cunningham to use sulfapyridine for the control of the troublesome postoperative secondary tonsillar hemorrhage, with uniformly excellent results. He also successfully employed sulfapyridine powder by insufflation in the control of persistent bleeding in a case of bronchial erosion. He suggested that the drug might be of value when locally applied to superficial abrasions, such as brush burns.

Cunningham's report led me to use sulfapyridine powder locally in treatment of a number of diseases. Following are 3 illustrative cases.

REPORT OF CASES

Case 1.—H. A. B., a white man aged 28, presented a severe telangiectatic rosacea of the tip of the nose. About half of the vessels were removed by scarification with an electrosurgical cutting current. This was followed by a persistent oozing for five hours. Sulfapyridine powder was unobtainable from any source on that day. Ten weeks later, after persuasion, he permitted the remaining vessels to be treated with a cutting current. Again a persistent oozing ensued, which ceased instantaneously after application of sulfapyridine powder.

Case 2.—S. K., a white woman aged 68, presented an oozing granulating lesion 1 cm. in diameter of the lower lip. Two weeks earlier a keratosis had been removed from the lower lip by her physician. This was followed by a persistent uncontrolled slow bleeding. When I saw her she was panic stricken and exhausted from loss of sleep. The oozing ceased immediately after application of sulfapyridine powder, and healing proceeded uneventfully.

Case 3.—H. W., a white man aged 65, presented a large pyogenic granuloma of the right forearm. This was removed with a Post cautery. As is sometimes the case after removal of a pyogenic granuloma of large size, persistent oozing occurred, which was easily controlled by the application of sulfapyridine powder.

COMMENT

The local application of sulfapyridine powder to wounds after removal of lesions by electrodesiccation, cutting current or cautery is especially useful in producing hemostasis. The surface of the wounds becomes hard and dry, and the wounds heal without infection. The use of sulfapyridine powder is superior to a solution of gentian violet medicinal, which is often used.

CONCLUSION

The local application of sulfapyridine powder to produce hemostasis is extremely satisfactory and deserves wider use.

1930 Wilshire Boulevard.

1. Cunningham, B. P.: Clinical and Experimental Studies with Sulfapyridine as a Hemostatic Agent, in Collected Papers of the Mayo Clinic, Philadelphia, W. B. Saunders Company, 1943, vol. 34, p. 12.

2. Since sulfamethylthiazole was found by various investigators to produce toxic effects, it is no longer available on the market.

Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

THE "LUPUS ERYTHEMATOSUS" CONCEPT: AN ATTEMPT AT INTEGRATION. JOHN H. STOKES, HERMAN BEERMAN and NORMAN R. INGRAHAM, Am. J. M. Sc. **207**:540 (April) 1944.

Stokes and his associates attempt to summarize and clarify recent suggestions as to the nature, cause and cure of lupus erythematosus. They look at the disease in the light of allergic reactions to infection, regarding the chronic discoid form as related to the follicular "ids" and the systemic form as an expression of vascular injury and allergy. They note the reports of observers who regard the cellular and connective tissue changes as manifestations of allergy but point out that there is not as yet a general acceptance of colloid degeneration as a sign of allergic reaction. Discoid lupus erythematosus can be hypothetically accounted for as follicular (seborrheic) infection plus allergic reaction to that infection (yeasts and staphylococci).

Dissemination of a discoid or follicular erythematous lupus with the appearance of desquamative patches with follicular atrophy over other parts of the body is simply an extension of the follicular "id" beyond its conventional locus, under conditions affecting the general allergic state of the individual. On the other hand, the reaction that underlies the chronic discoid process may at a suitable provocation pass over into the field of vasculoallergic manifestations and assume the far graver characteristics of the so-called acute disseminating type of the disease. The authors state that as to the nature of the infection to which allergy develops or exists no absolute decision can be had at this time and the contribution of a concept of infection-allergy to the treatment of lupus erythematosus is largely negative. They regard therapy with bismuth as equally effective as and safer than treatment with gold. They warn that sulfonamide compounds must be used with the utmost caution, though they are helpful in some cases.

Reviewing the suggestions of others, that lupus erythematosus may be subject to endocrine influences, they state that "it would appear justifiable to undertake further study of possible relationships between gonadal hormones and lupus erythematosus and to investigate the possible usefulness of castration in female patients more extensively."

LYNCH, St. Paul.

CANCER ASSOCIATED WITH ACANTHOSIS NIGRICANS: REVIEW OF LITERATURE AND REPORT OF A CASE OF ACANTHOSIS NIGRICANS WITH CANCER OF THE BREAST. HELEN OLLENDORFF CURTH, Arch. Surg. **47**:517 (Dec.) 1943.

The case of a 47 year old woman who had cancer of the right breast and acanthosis nigricans is presented. After removal of the breast the acanthosis nigricans tended to subside for a while. The patient died about one and one-half years after operation. Permission for opening of the thoracic cavity was not given. Widespread metastases were found in the liver, left kidney and left adrenal gland. Acanthosis nigricans had reappeared a few months after operation and had spread over wide areas of the body.

This is the ninth case of mammary cancer associated with acanthosis nigricans. The high malignancy of this tumor corresponds with the character seen in all carcinomas accompanying acanthosis nigricans. A complete review of all cases published is given, and all tumors accompanying acanthosis nigricans are tabulated.

Benign and malignant acanthosis nigricans are identical. Instances in which characteristics of the benign and of the malignant types were shown successively or simultaneously are presented. The presence of acanthosis nigricans and cancer in the same patient is not coincidental, since (1) the percentage of cancer in patients with acanthosis nigricans is extremely high; (2) the two diseases become manifest at about the same time and run a parallel course, and (3) many young persons suffer from cancer and acanthosis nigricans.

Previous concepts of the causation of acanthosis nigricans, such as those attributing it to disturbances of the sympathetic nervous system or of the adrenals or other endocrine glands, should be discounted and cancer considered the essential etiologic factor of the disease. In cases of malignant acanthosis nigricans some properties of the tumor may activate the cutaneous lesions. In the benign type the same role of activation seems to be played by one of the sex hormones. There are a large number of cases of benign acanthosis nigricans on record in which the disease appeared or began to spread at puberty. The role of cancer in the family history of patients with acanthosis nigricans, the type of cancers that have been associated with it and the chronologic independence of acanthosis nigricans and cancer speak for a genetic relationship between the two diseases. Criteria of benign and malignant acanthosis nigricans are given.

CURTH, New York.

OCULAR ROSACEA. G. WISE, Am. J. Ophth. **26**:591 (June) 1943.

The present study of rosacea was undertaken primarily to evaluate the various etiologic possibilities, in particular the theory that rosacea is due to riboflavin deficiency. The following conclusions are reached.

"Ocular rosacea occurs following facial rosacea and both are manifestations of the same disease.

"At present the fundamental cause of rosacea is unknown.

"Rosacea is not a manifestation of riboflavin deficiency.

"Previously considered causes of rosacea, such as gastrointestinal disturbances, focal infection, endocrine and other disorders, are not fundamental etiologically, but in some cases may be transient aggravating factors.

"Rosacea probably does not occur in the Negro race.

"Lowered gastric acidity is neither specific for rosacea nor nearly so frequent an accompaniment of it as has previously been thought. Its presence is of no special significance.

"Hyaluronic [acid] ester is not decreased in the cornea of the rat that has become vascularized due to riboflavin deficiency.

"The importance of secondary infection in cases of ocular rosacea has been neglected in the past.

"Except in the unusual and rare cases of severe ocular rosacea without secondary infection, most of the distressing symptoms and sequelae of ocular rosacea are due to secondary infection with staphylococci.

"The secondary infection in ocular rosacea can be controlled in almost all cases with 5 per cent sulfathiazole or sulfadiazine ointment, used locally several times daily.

"Rosacea probably is due to some factor causing vasodilatation in the facial area."

W. ZENTMAYER. [ARCH. OPHTH.]

RAT-BITE FEVER: COMPARISON OF THE SPIROCHETAL (SODOKU) AND BACILLARY (HAVERHILL FEVER) FORMS. C. MICHAEL WITZBERGER and HERBERT G. COHEN, Arch. Pediat. **61**:123 (March) 1944.

Witzberger and Cohen feel that in this period of global transportation physicians should acquaint themselves with the two clinical syndromes of rat bite fever. Sodoku is caused by Spirochaeta morsus muris, and Haverhill fever is due to Streptobacillus moniliformis. The authors have prepared a short table showing a comparison of these two syndromes which may serve as an aid in differential diagnosis. The two syndromes are discussed separately, and a case of each variety is presented. In the sodoku form a chancre-like ulceration develops at the site of the bite, which is followed by regional lymphadenitis and later by a generalized maculopapular rash which fades during the afebrile periods. In the Haverhill form there is no subsequent induration at the site of the bite and the eruption is at first macular and later petechial. In this form there develops a metastatic arthritis as a result of generalized septicemia.

GELBER, Los Angeles.

TREATMENT OF ACNE VULGARIS. CHARLES H. BIRNBERG and CHARLES R. REIN, J. Clin. Endocrinol. **4**:65 (Feb.) 1944.

Birnberg and Rein report definite improvement of acne in 14 of 17 patients treated by injections of serum from pregnant mares. Six of these patients showed hirsutism which was not altered by treatment, and 2 gave abnormal results on hormonal studies. Most of them presented evidence of some degree of hypopituitarism, and all of them had some associated menstrual disturbance. The authors do not infer that pregnant mare serum is a cure for acne vulgaris, but they suggest that in any case in which the disease is influenced by the menstrual cycle there should be thorough endocrine study and treatment should be instituted according to the results of this study.

LYNCH, St. Paul.

THE VELOCITIES OF INHIBITION OF BACTERIAL GROWTH BY SULFONAMIDE AND OF THE ANTAGONISTIC EFFECT BY P-AMINOBENZOIC ACID. JULIUS HIRSCH, J. Immunol. **48**:199 (March) 1944.

According to Fildes' theory, the effect of sulfonamides is based on the structural similarity with paraaminobenzoic acid. Paraaminobenzoic acid (an "essential metabolite") and sulfonamide compounds compete with each other at sites within the cells important for the process of multiplication. According to this theory, inhibition of growth by sulfonamide compounds and the reversal of this inhibition by paraaminobenzoic acid must both represent reversible reactions.

On the basis of the results of his experiments, the author believes that the interference with the action of paraaminobenzoic acid by sulfonamide compounds postulated by Fildes and the experimentally demonstrable interference with the sulfonamide effect by paraaminobenzoic acid cannot be considered as equivalent processes caused by a similar reversible reaction. This becomes the more evident, he thinks, if the concentrations of the participating substances are considered. He found that inhibition of growth is instantly antagonized by a concentration ratio of 1 mol of paraaminobenzoic acid to 10 mols of Irgafen (Gergy 867, N_1-3,4-dimethylbenzoylsulfanilamide). He could make no definite statements concerning the concentration ratios of the two competitors in an inhibitive experiment. If paraaminobenzoic acid is produced at all in a synthetic medium, the concentration is certainly several powers of 10 less than the concentration of N_1-3,4-dimethylbenzoylsulfanilamide, which, however, acts only very slowly regardless of the quantitative advantage. His findings suggest that the inhibition of bacterial proliferation by sulfonamide compounds is a more complex process than the reversal of inhibition by paraaminobenzoic acid. The inhibiting effect of sulfonamide has a lag period of one to two hours; in contrast to this, the bacteriostatic effect of sulfonamide compounds is instantly antagonized by addition of paraaminobenzoic acid.

THE ACTION OF DETERGENTS ON STAPHYLOCOCCAL INFECTIONS OF THE CHORIO-ALLANTOIS OF THE CHICK EMBRYO. T. W. GREEN, J. Infect. Dis. **74**:37 (Jan.-Feb.) 1944.

The widespread interest in the antibacterial effects of detergents is evident from the increasing number of publications dealing with their action. Some authors have found that the bacteriostatic and germicidal action of the cationic detergents is much greater than that of the anionic agents. Because of these observations the author made a study of the comparative therapeutic action of these two classes of detergents, using the chick embryo technic, which has proved successful for the in vivo testing of various therapeutic agents.

He found that none of the anionic agents were therapeutically active while most of the cationic agents exerted a demonstrable therapeutic effect. Replacement of the chloride or bromide ion by the iodide ion in several compounds resulted in a lower degree of therapeutic activity. Variation in the length of the carbon chain (12 to 18) in the alkyl groups of a homologous series of compounds resulted in no great changes in therapeutic effectiveness. Because several compounds similar in structure and degree of germicidal action exhibited great differences in effectiveness in the egg, the author concluded that the degree of germicidal action of a compound is not a sound basis for prediction of relative therapeutic effectiveness even within such a restricted group as the cationic detergents. He feels that the utility of the infected chick embryo as an adjunct in the evaluation of disinfectants is well demonstrated by his experiments.

CORNBLEET, Chicago.

A STUDY OF OILS USED FOR INTRAMUSCULAR INJECTIONS: A STUDY OF THE PHYSICAL, CHEMICAL AND BIOLOGIC FACTORS. WILLIS E. BROWN, VIOLET M. WILDER and PAULINE SCHWARTZ, J. Lab. & Clin. Med. **29**:259 (March) 1944.

The authors undertook to investigate the factors which should guide a physician in the selection of the oil vehicle for intramuscular injections.

The suggested criteria for the ideal oil included physical, chemical and biologic specifications, which are: 1. Chemically the oil should be stable and neutral in reaction and should not react with medication to form toxic products. 2. Biologically it should be inert and nonirritating. It should be essentially free of antigenic properties and be rapidly absorbed from living tissue, leaving no residue. 3. Physically it should be a good solvent or dispensing medium and not too viscid to pass readily through the needle. Extremes in temperature should not alter any of these features.

Using these criteria, they studied four commonly used oils (corn, peanut, sesame and cottonseed). The antigenic study was made on 20 patients who received at weekly intervals two injections of each of the four oils. Approximately two months later these patients were tested by the patch and intracutaneous tests. The biologic reaction was investigated by injecting the oils intramuscularly into the large muscles of the extremities of rats and rabbits. The muscular reactions were studied microscopically by means of frozen and stained sections. The intensity of the reaction was judged by (*a*) the accumulation of leukocytes, (*b*) the formation of oil cysts, and (*c*) the deposition of fibrin. They found that sesame and corn oils are superior to peanut and cottonseed oils for intramuscular injections, for they are (1) more suitable physically and chemically for this purpose, (2) more quickly absorbed from the tissue, (3) less antigenic, and (4) less irritating to tissue.

GELBER, Los Angeles.

SKIN DISEASE OF THE NEWBORN INFANT. MACHTELD E. SANO, J. Pediat. **23**:280 (Sept.) 1943.

As a result of an intensive study of a case of desquamative erythroderma (Leiner's disease) correlated with an extensive review of the literature, the author concludes that the underlying cause of desquamative erythroderma (Leiner's disease) and exfoliative dermatitis (Ritter's disease) is a temporary dysfunction of the endocrine system. The dysfunction in the majority of infants probably originates in the mother, who has to adapt herself physiologically to the demands put on her endocrine system during pregnancy.

The histologic examination of the endocrine glands, illustrated by photomicrographs, and biochemical studies of the case confirm some of the observations reported in the literature.

The conditions observed in this detailed clinical and histopathologic study indicate that desquamative erythroderma cannot be considered as an entity but that it is rather as a manifestation of an underlying cause responsible also for exfoliative dermatitis and possibly other cutaneous diseases in the newborn infant.

SONTAG, Yellow Springs, Ohio.
[AM. J. DIS. CHILD.]

FAVUS IN MASSACHUSETTS: A REPORT OF TWO CASES. G. E. MORRIS, New England J. Med. **230**:667 (June 1) 1944.

Morris reports 2 cases of favus; in 1 the patient was a 17 year old girl and in the other an 18 year old girl. In both of them direct examination and cultures revealed Achorion schoenleinii, also demonstrated by the characteristic fluorescence under the Wood light.

Because of the usual therapeutic difficulty and the known recurrences even after roentgen epilation, Morris used a solution of 10 per cent thymol in chloroform, twice daily, a shampoo twice weekly and manual epilation at home and once weekly at the clinic under the Wood light.

One year of such treatment has been successful in both cases.

ECZEMA VACCINATUM. F. C. COMBES and H. T. BEHRMAN, New York State J. Med. **43**:2283, 1943.

Combes and Behrman report a case of eczema vaccinatum which developed on the face of a 24 year old man with chronic folliculitis of the beard after contact with recently vaccinated members of the family. The danger of vaccination in the presence of a cutaneous disease is emphasized.

CUTANEOUS MANIFESTATIONS OF TUBERCULOSIS. A. C. CIPOLLARO, New York State J. Med. **44**:1557, 1944.

Tuberculosis of the skin is divided in two main groups, the localized and the hematogenous. Etiology, clinical appearance and therapy are discussed for the various types.

RONCHESE, Providence, R. I.

MONILIASIS OF THE EXTERNAL EAR CANAL. WILLIAM L. DOBES, South. M. J. **36**:614 (Sept.) 1943.

Dobes calls attention to the work that has been done and the progress made in attempts to separate and classify the saprophytic and the pathogenic fungi. The yeastlike fungi most frequently encountered are: (1) Monilia, (2) Cryptococcus and (3) Mycoderma. Monilia is subdivided into several strains, of which Monilia albicans is considered pathogenic, while the other strains are considered saprophytic. In reviewing the current literature the author found only two articles in which reference was made to involvement of the external canal by M. albicans. He reports a case of disease of the external canal due to M. albicans. The patient was treated with a 2 per cent solution of methylrosaniline (gentian violet) at daily intervals, and the lesion was healed within ten days. Local applications of 1 per cent mercury bichloride in 50 per cent alcohol and of mercurous iodide in alcohol are sometimes used in treating this type of infection.

SINGLETON, Dallas, Texas. [ARCH. OTOLARYNG.]

A PLEA FOR THE STANDARDIZATION OF THE LEPROMIN TEST. JOHN W. FIELDING and ROBERT G. COCHRANE, M. J. Australia **1**:313 (April 8) 1944.

The active element for the lepromin test is contained in the bacillary content of the emulsions. Effective prolonged grinding for the separation of bacilli from tissue element is all important. Standardization of the bacillary content of the emulsions is essential in order to obtain uniform reactions. The Breed milk count (bacteria) is advocated when emulsions of a low bacillary content are to be standardized. A combined Breed-Owen count method may be used for emulsions of low or high bacillary content. When used by the authors the Breed-Owen count has given reasonable satisfaction.

THE TREATMENT OF CARCINOMA OF THE DORSUM OF THE HAND. P. D. BRADDON, M. J. Australia **1**:368 (April 22) 1944.

Early epitheliomas of the dorsum of the hand are almost invariably of the squamous cell variety. In some thousands of cases only 6 instances of basal cell epitheliomas were encountered. This type of lesion, up to a little over 2 cm. in diameter, is best treated surgically.

Advanced epitheliomas are growths over 2 cm. in diameter. Two hundred patients with advanced epitheliomas were treated by radon molds with consistently excellent results. In the treatment of this lesion, radium or radon needles or seeds should never be implanted. The dose delivered is always 6,000 r over a minimum period of ten days and a maximum period of sixteen days.

CREEPING ERUPTION (LARVA MIGRANS). JAMES F. HUGHES, M. J. Australia **1**:393 (April 29) 1944.

Hughes reports 2 cases of larva migrans. He has found three forms of treatment reliable. Excision of the migrating larva, refrigeration with ethyl chloride spray for two minutes and application of solid carbon dioxide were effective procedures.

THE USE OF THE CHORIO-ALLANTOIS OF THE DEVELOPING CHICK EMBRYO IN THE DIAGNOSIS OF SMALLPOX. E. A. NORTH, J. A. BROBEN and A. H. MENGONI, M. J. Australia **1**:437 (May 13) 1944.

By the use of the developing egg as a medium, variola and vaccinia viruses may be distinguished. In addition to its greater sensitivity compared with the rabbit's cornea, the developing chick membrane permits differentiation of variola and vaccinia, whereas a positive reaction to the Paul test is given by both variola and vaccinia viruses. The appearance of the foci produced on the chorioallantois enables distinction to be made between variola virus and the strains of vaccinia virus.

THE LEPROMIN TEST IN LABORATORY ANIMALS. J. W. FIELDING, M. J. Australia **1**:439 (May 13) 1944.

The lepromin test in animals gave a variable result except in the case of rats, which consistently failed to react. This was true with emulsions both from human beings and from rats.

HENSCHEL, Denver.

TREATMENT OF SCABIES WITH AN EMULSION OF R[OTE]TENONE. E. P. WOODROW, South African M. J. **17**:233 (Aug. 14) 1943.

The author reports excellent results in the treatment of 225 patients with scabies with an emulsion of rotenone. Of the 177 patients who returned for observation, all except 10 were cured by one course of treatment. Of the 10 who relapsed, 9 were cured after one further course of treatment and the tenth required a third course. The solution used on all infants under 9 months of age and on many adults with mild infestations consisted of 1 per cent rotenone and 3 per cent chloroform in mucilage of chondrus. For severe infestations in adults the percentages of rotenone and chloroform were doubled. The lotion was applied twice the first day and twice the second, a bath being taken before the initial application but not again until the third day.

GONCE, Madison, Wis. [AM. J. DIS. CHILD.]

EAGLE'S FLOCCULATION TEST OF THE SPINAL FLUID. JOÃO BAPTISTA DOS REIS and WALDEMAN CARDOSO. Arq. assist. psicopat. estad. São Paulo **7**:207 (March-June) 1942.

The authors used the Eagle flocculation test in 100 cases of neurosyphilis. In cases of nontreated neurosyphilis the Eagle flocculation and the Wassermann test were equally sensitive. In cases of old, unsuccessfully treated neurosyphilis the Eagle test appeared to be more sensitive than the Wassermann test. In cases in which the disease was under treatment there was a significant parallelism between the Eagle and the Wassermann test. The results of the Wassermann and of the Eagle test were in disagreement in only 7 of 40 cases.

SAVITSKY, New York. [ARCH. NEUROL. & PSYCHIAT.]

Society Transactions

MANHATTAN DERMATOLOGIC SOCIETY

ANTHONY C. CIPOLLARO, M.D., *President*

WILBERT SACHS, M.D., *Secretary*

Jan. 11, 1944

Elephenatiasis of the Scrotum and Left Leg: Five Year Use of Sulfonamide Compounds. Presented by DR. E. WILLIAM ABRAMOWITZ.

I. R., a 58 year old merchant born in Hungary and married, has three children alive and well. He has been in the United States for forty-two years. There is no history of any abnormalities in his family. When he was 12 years old and living near Budapest, an enlargement developed on the left side of his scrotum. In 1903 he was operated on at Mount Sinai Hospital, in New York city, for enlargement of the right side of the scrotum. He made a stormy recovery.

In 1922 the patient noted the development of an oozing dermatitis of the scrotum, which was rather persistent. In 1925 he made a one month trip to Louisiana, South Carolina, Alabama and Tennessee. The dermatitis became aggravated in 1932, accompanied by fever and chills and a definite increase in the size of the scrotum. After that he had on the average four attacks of fever (temperature 103 to 104 F.) a year, which lasted about three or four days. The swelling of the scrotum continued to increase, and in 1939 swelling of the left leg began to develop.

In 1939 he began to take five tablets of of sulfanilamide daily for three or four days during the febrile attacks, which recurred about every five to six weeks. He was referred to me in April 1941, and I prescribed azosulfamide and later sulfathiazole instead of sulfanilamide.

There is a tremendous enlargement of the scrotum, which presents a reddened, thin skin. It measures 20 by 12 inches (50 by 30 cm.). The skin of the penis is swollen, and the glans is retracted. Pitting is present in these areas as well as on the left leg. There is no dermatitis of the leg.

The patient had a 4 plus reaction to staphylococcus toxoid, and a 1 plus reaction to hemolyticus and viridans streptococci. At one time there was a slight trace of sugar in his urine, but this has since disappeared. Examination of the blood for filariae was unsuccessful.

Besides the sulfathiazole, the patient received fractional roentgen ray therapy and injections of staphylococcus modified toxoid. Under this treatment no febrile or scrotal reactions recurred from April 1941 until August 15 of that year, and they occurred then because the use of sulfathiazole had been discontinued. There were no symptoms from August 1941 until May 1942, when he stopped taking the drug for about three or four months. A relapse developed in December 1942, at which time he had discontinued the drug for one year. Another attack occurred in February 1943. Then he began to take the drug and vaccine again. In October 1943 he once more stopped taking the drug, and another attack developed in December 1943.

The roentgen therapy and the staphylococcus toxoid (when given without the sulfathiazole) did not prevent recurrences. Further tests for filariae will be made, and surgical consultation is advised regarding operation to relieve the difficulty in urination caused by the retraction of the penis and also to reduce the size of the scrotum.

DISCUSSION

DR. MAX SCHEER: Filariasis is occasionally seen in temperate climates. I think that an examination of the blood for filariae should be repeated, especially at night. I doubt if the disease is present, but it should be excluded.

DR. HERMAN SHARLIT: If there is no blood infection behind this disability, why cannot some plastic operation be performed to make the patient comfortable?

DR. JOSEPH R. RICCHIUTI (by invitation): I have seen a good many patients with filariasis coming back from the southwest Pacific. They have lost most of the elephantiasis after their return to the States, only fibrosis remaining. In none of them have I been able to find filariae. Associated with the infection one frequently sees a recurrent generalized urticaria.

DR. FRED WISE: I would like to inquire from the members whether this type of case is favorable for operative procedure.

DR. E. WILLIAM ABRAMOWITZ: The Kondoleon operation removes tissue down to the fascia of the muscles in elephantiasis of the legs. The disease has a tendency to recur, however, and subsequent operation may be necessary. The recent literature indicates that patients affected with filariasis may carry the organisms in the blood without symptoms and without blockage. It is not the filariae alone that cause the trouble, apparently, but the attacks of lymphangitis due to secondary invaders which also appear in cases without filariae. One has to keep on testing for filariae, not only at night and not only in the blood but in aspirated lymph tissue. I am against the indiscriminate administration of the sulfonamide drugs, but here is a patient who cannot get along without them and who has taken them for five years without any trouble—sulfanilamide, azosulfamide, sulfathiazole, sulfapyridine and sulfadiazine.

A Case for Diagnosis (Pemphigus?). Presented by DR. E. WILLIAM ABRAMOWITZ.

Lieutenant A. J., aged 23, had an ulcer on the buccal surface of the lower lip in June 1941. The lesion was treated with silver nitrate and healed in one week. Shortly after this, however, new ulcers appeared in the mouth, on the tongue and on the soft palate. The lesions were painful; they lasted about seven days, healed and were followed by a new crop. Six months later, in January 1943, the ulcers began to appear in the mouth as bullae and followed the same course. Because a smear showed Vincent's bacilli, two partially impacted wisdom teeth were extracted. In September 1943, a small vesicle containing clear fluid appeared on the normal skin of the right thigh. A similar vesicle appeared on the left shoulder one month later. During the next four months crops of vesicles and bullae appeared on the face, shoulders and wrist. The patient

states that itching precedes the appearance of a vesicle. Recently he noticed that his nose contained a bloody crust. Examination showed a nasal perforation with ulceration of the mucous membrane surrounding this site.

Exhaustive studies concerning intake of drugs showed that the patient occasionally took acetylsalicylic acid, Ex-Lax and phenobarbital. He used Squibb's tooth paste (pink) and occasionally drank Chianti wine. A test dose of phenolphthalein produced large bullous lesions with surrounding erythema on the glans penis within twenty-four hours. There was no exacerbation of the oral lesions.

In July 1943, an apical abscess was found in a lateral incisor tooth which was extracted; culture showed Streptococcus viridans.

On Jan. 19, 1944 there was a sudden appearance of numerous pruritic pea-sized erythematous macules on the palms.

The general physical examination gave normal results except for the skin. On the face, right shoulder and left wrist there are a number of healing ulcerations. There are several tiny vesicles on the soft palate. There are pea-sized erythematous macular lesions on the palms. There has been no loss of weight.

Results of urinalysis and a blood count were normal, and the Kahn reaction was negative. A patch test with 30 per cent solution of potassium iodide elicited a negative reaction. The calcium content of the blood was 11.4 mg. per hundred cubic centimeters, and the phosphorus content was 4.2 mg. A smear from vesicle fluid showed many polymorphonuclear cells but no eosinophils, and culture showed a Streptococcus viridans.

Histologic examination showed the vessels of the middle and upper parts of the cutis to be dilated, many being filled with blood elements. There was some edema of the vessel walls and swelling of the intima and some disruption of the vessel walls in places. About the vessels was also a moderate small round cell and wandering connective tissue cell infiltration with many polymorphonuclear leukocytes. Within the epidermis was a tremendous cavity filled with polymorphonuclear leukocytes, many of which were eosinophils. The diagnosis was pemphigus.

The treatment so far has been to eliminate all drugs. The patient is taking 100,000 U. S. P. units of vitamin A and 200,000 U. S. P. units of vitamin D daily. He has had fewer lesions in the last two weeks.

NOTE.—The patient remained clear of lesions for six weeks and was then given a therapeutic trial of phenolphthalein, acetylsalicylic acid and acetophenetidin. No new lesions resulted. There has been a three month interval of freedom from lesions.

DISCUSSION

DR. FRED WISE: I do not think that these are sufficient clinical changes to justify the diagnosis of pemphigus vulgaris in this patient.

DR. ISADORE ROSEN: In view of the facts that the patient had similar lesions a year and a half ago, that there is a history of appearance and disappearance of lesions and that there are lesions on the palms, I think that he is suffering from erythema multiforme and not pemphigus. Pemphigus is usually a progressive disease and does not show periods of spontaneous remission as in this case.

DR. WILBERT SACHS: I examined the sections in this case, and to me there is presented a picture of pemphigus. It is a typical intraepidermic bullous lesion, which to me would be against a diagnosis of drug eruption or any other type of erythema multiforme. The epidermis was split, and there were some eosinophils in the bullous lesions; the character of the vessels underneath also suggested pemphigus.

DR. FRED WISE: Tense bullae may appear in pemphigus, but I do not recall the occurrence of macular lesions of the palms in that disease.

DR. HERMAN SHARLIT: If there is a question of the patient's having reacted to phenolphthalein once, that should be verified. If this is true, it is fair to assume that even if the eruption is not due to phenolphthalein it is due to some process that is not pemphigus.

DR. JOSEPH F. RICCHIUTI (by invitation): The macular lesions on the palms appeared tonight, and I saw them for the first time at 7 p. m. Dr. Abramowitz and I have been reluctant to accept a diagnosis of pemphigus, having thought of erythema multiforme of the bullous type, and it is only our studies, the lack of a history of drug ingestion, the histologic examination and the recurrence of the lesions that have led us to that opinion. I still feel there is a possibility of a toxic erythema of the bullous type.

DR. MAURICE J. COSTELLO: Has the Pels-Marcht phytopharmacologic test been performed?

DR. JOSEPH F. RICCHIUTI: No.

DR. E. WILLIAM ABRAMOWITZ: My opinion just now is that the diagnosis is undecided, but I do not think the patient has pemphigus.

Eosinophilic Granuloma. Presented by DR. GEORGE M. LEWIS.

M. R., a man aged 47, was previously presented before the Manhattan Dermatologic Society, on Oct. 13, 1942, and before the New York Academy of Medicine, Section of Dermatology and Syphilis, on May 3, 1943.

DISCUSSION

DR. FRED WISE: An Italian dermatologist presented two articles on eosinophilic tumor formation under the name of granuloma eosinophilicum. Dr. Lewis tells me that he is acquainted with the articles but that this patient's lesions are not identical with those described.

DR. JACK WOLF: Eosinophilic tumors of bone have also been described. It might be advisable to make roentgenograms of the long bones and to perform sternal puncture.

DR. E. WILLIAM ABRAMOWITZ: I should like to offer a diagnosis of an unusual form of mycosis fungoides. I think that cases have been described which present little else but eosinophilic tumors.

DR. WILBERT SACHS: I have never seen a slide in which there were pure eosinophils in the tissue. I should assume, however, that in such cases, whether the tumors arise in the bone or in the skin, they would be related more to some form of leukemia or mycosis fungoides than to any other disease with which I am acquainted.

DR. GEORGE M. LEWIS: I have followed this man carefully for several years without establishing any primary focus for the eruption. His blood picture is not abnormal except for a slight increase in the eosinophils. It might be good procedure to carry out Dr. Wolf's suggestion. Regarding the possibility of mycosis fungoides, the tumors are not radiosensitive, and the lesions develop and disappear in a manner different from those of mycosis fungoides. Dissolution occurs usually by softening of the lesions, and then they entirely disappear within a week.

Exudative Discoid and Lichenoid Chronic Dermatosis. Presented by DR. MAURICE J. COSTELLO.

B. K., a salesman aged 43, was examined by me in July 1941, at which time he stated that he had had a pruritic eruption for six months, during which period he had lost 10 pounds (4.5 Kg.). There is no history of personal or familial hypersensitivity. The eruption began on the anterior aspect of the left leg and later became generalized, appearing on the inner aspect of the arms, sides of the chest, buttocks, scrotum and thighs. He was admitted to Lenox Hill Hospital at that time, where he was given a series of intravenous injections of typhoid vaccine. Coal tar paste was applied. He improved during his stay in the hospital but was not completely cured when discharged.

Since that time the patient has received occasional low voltage roentgen ray treatments, with temporary relief. In addition, sedatives, such as sodium amytal and tablets of three bromides N. F., have been necessary to relieve the intense pruritus. Exposure to sunlight at the beach in the summertime and a trip to Florida have given several long remissions.

The eruption has passed through several phases. First there was pruritus without eruption, then an eczematoid and exudative stage and finally the present phase, which presents discoid lesions on the back as well as on the aforementioned sites. For the past two years he has had a persistent plaquelike, raised, oozing erythematous eruption on the penis. Roentgenograms of the abdomen and the gastrointestinal tract showed a duodenal ulcer in 1941. Blood counts have been essentially normal. On one occasion there was an elevation of leukocytes to 19,250. A chemical examination of the blood showed: urea nitrogen 8.2 mg. per hundred cubic centimeters, creatinine 0.5 mg., uric acid 4.1 mg., sugar 123 mg. and carbon dioxide-combining power 61.4.

DISCUSSION

DR. JACK WOLF: I had occasion to see this man about two and a half years ago. He then gave a history of severe pruritus of one year's duration; he did not have a single lesion on the body at that time.

DR. ISADORE ROSEN: I agree with the diagnosis of chronic exudative lichenoid and discoid dermatosis. The clinical features of the cutaneous manifestations resemble first a dermatitis venenata, and subsequently the lesions go through various stages of development, as described in the history. They may at any time resemble mycosis fungoides or one of the forms of lymphoblastoma.

DR. HERMAN SHARLIT: Is there not a feeling that in some cases the disease is on a dermatitis venenata basis?

DR. GEORGE C. ANDREWS: I have the impression that in many such cases there is a generalized pruritus before the cutaneous lesions develop. Dr. Costello says that the patient is of a high-strung, nervous disposition. I suspect that a neurosis is the underlying factor in many cases.

DR. MAX SCHEER: Many of these patients are high-strung and nervous, which in all probability is a result of continuous and intolerable itching. In some cases the disease begins as dermatitis venenata or as a pityriasis-rosea-like eruption. I cannot get away from the feeling that some of these are cases of dermatitis venenata, and I strongly suspect that in a number of cases that I have observed the etiologic factor was the naphthalene used to keep moths away from the clothing. I saw 1 patient get well when his apartment was thoroughly cleared of naphthalene balls.

DR. MAURICE J. COSTELLO: This patient on one occasion went to Florida, exposed his body to sunlight and salt water and forgot his worries, and the eruption cleared. I agree with Dr. Andrews that the patient is of a high-strung, neurotic type, having difficulty in the struggle for existence. All the patients I have seen suffering with this disease have been Jewish men of neurotic temperament between the ages of 35 and 40 years; most of them worked in the clothing industry, and they were improved by a change of climate or hospitalization. This man's eruption has passed through three stages: (1) pruritic, (2) eczematoid and exudative and (3) lichenoid and discoid. A biopsy performed by Dr. Wilbert Sachs confirmed the diagnosis. The vessels throughout the middle and upper layers of the cutis were dilated, and about them was a pronounced cellular infiltration. The overlying epidermis was acanthotic, and at one point there was a Monro abscess. The cellular infiltration was composed of small round cells, numerous plasma cells and some epithelioid cells. A considerable amount of pigment was present. There was neither reticulum nor mitotic figures, nor were there any Pautrier abscesses or clumping of the nuclei.

Disseminated Sarcoid with Pharyngeal Lesions. Presented by DR. FRED WISE.

M. C., a woman aged 39, referred by Dr. Laird S. Van Dyck, registered at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Jan. 12, 1943, with lesions of four years' duration. She was born in Puerto Rico, and has been in the United States for seventeen years. She has three children who are living and "well." The patient gives no history of previous cutaneous disease but had measles and chickenpox during childhood and pneumonia ten years ago. She feels dizzy and tired at times but is otherwise in fairly good health. She has been hoarse for the past year.

The eruption began four years ago as three pea-sized growths on the left cheek. A year ago similar lesions developed on the tip of the nose, upper lip and the root of the nose. Six months ago the other lesions appeared.

The lesions are located at the root and tip of the nose and on the right supraorbital region, both cheeks, upper lip, middle of the pinna of the right ear and lobule, right breast, arms and legs. They are almost symmetrically distributed and consist of irregular nodules from the size of a pea to that of a bean and larger, of slightly purplish hue and somewhat raised above the surface. They are soft, well defined, easily compressible and painful to touch. One large lesion involves the tip and the right ala nasi. The lesions on the left cheek have healed with some depressed scarring. The patient has a soft bean-sized growth on the left side of the pharyngeal wall. There are telangiectatic capillaries on the lesion of the nose.

The Wassermann reaction was negative, and urinalyses gave normal results. The hemogram showed a moderate anemia, a leukocyte count of 4,250, with 6 polymorphonuclear eosinophils, 7 monocytes and 14 (normal 3 to 5) band forms per hundred cells. Chemical examination of the whole blood gave normal values for urea nitrogen, nonprotein nitrogen, uric acid and dextrose. Examination of the blood serum showed: total proteins, 7.6 mg. per hundred cubic centimeters; albumin, 4.2 mg.; globulin, 3.4 mg. (normal 2 to 3 mg.); ratio, 1.2:1 (normal 1.6 to 2.0:1). The ascorbic acid concentration in the blood plasma was 0.2 mg. per hundred cubic centimeters (normal 0.7 to 1.4 mg.). The sedimentation rate was 97 mg. per hour by the

Westergren method (normal in female 15 mm. per hour). Examination of the nasal smear was negative for lepra bacilli. Intracutaneous tuberculin tests with concentration as low as 1:1,000 elicited negative reactions.

A histologic section showed a sarcoid-like reaction. The epidermis was thin and the rete pegs flattened. The basal border was intact except in one area, where the basal cells were disorganized. The entire cutis was occupied by an inflammatory reaction composed of epithelioid cells and a few round cells. The cytoplasm of many of the epithelioid cells showed vacuolation. Staining with carbolfuchsin did not reveal the presence of organisms.

Roentgenograms of the hands showed multiple areas of rarefaction of various sizes surrounded by zones of condensation in the cortexes of most of the phalanges. Though as a result of the cystic-like changes in the cortexes there was no expansion, here and there a slight subperiosteal outer cortical erosion was noted, being observed mainly in the middle phalanx of the middle finger of the right hand, with secondary soft tissue infiltration. Moderate soft tissue swelling above some of the interphalangeal articulations was also noted. The picture was considered to be such as is more frequently observed in sarcoidosis or granuloma other than tuberculous.

Examination of the thorax showed little evidence of pathologic change. A slight degree of hilar and root branch thickening, with interlobar accentuation, was observed on the right side. This was thought to be probably puerile in origin, with no evidence of recent parenchymatous infiltration. The heart was within the 10 per cent limit of normal.

Ophthalmologic examination gave normal results. Report of the neurologic examination on Oct. 8, 1943 by Dr. Stockfisch follows: "The neurologic picture was essentially normal except for a few signs. The interosseous muscles and the thenar eminences showed slight atrophy. There was some weakness in the opponens pollicis muscles. It is my opinion that this condition is incidental to general malnutrition and rheumatoid arthritis in the hands. I should say that there is no neurologic involvement."

Some of the lesions on the face were destroyed by electrodesiccation, but there has been recurrence.

DISCUSSION

DR. MAX SCHEER: I accept the diagnosis of sarcoid, but had I seen the lesions only, without knowing the result of the tuberculin test or of the roentgenograms of the hands, I should have believed that the lesions, especially the one on the nose, were typical of lupus vulgaris.

DR. FREDERICK REISS (by invitation): I saw the slide of this case, and the histologic picture was not at all indicative of leprosy. Referring to Dr. Sachs's remarks, I think it is true that there is often confusion about vacuolation. In the lepromatous type of leprosy, which is characterized by the richness of Hansen's bacilli, there are two kinds of vacuoles: one a globus and the other a degeneration of the reticuloendothelial (foam) cells. In such instances, if it were the lepromatous type of leprosy, one ought to find bacilli without difficulty. If it were the sarcoid type of leprosy, one would expect such trophic disturbances as would be visible clinically and sensory disturbances to verify it. Rarefaction of the bones does not exclude the sarcoid type of leprosy. Dr. Rabello, in Brazil, is almost convinced that what is called sarcoid is a mitigated form of Hansen's disease.

DR. FRED WISE: The question of leprosy was of course taken up by the men who examined the patient, and the disease was excluded. I think a degenerative process may be taking place in the muscles as in the bones, a cystic degeneration in the latter.

Acrodermatitis Continua. Presented by DR. GEORGE M. LEWIS.

F. C., a carpenter aged 58, removed a splinter from under the nail of his left ring finger eighteen months ago. Shortly afterward there was swelling and pain in the region, followed by separation of the nail and subsequently by inflammation of the region of the nail bed. Soon other fingers became considerably affected, the lesions being confined to the region of the nails. In the course of treatment he received dressings which appeared to immobilize his hand. A rash spread up the fingers and affected his hand and forearm. This was later treated with wet dressings, with good response. No lesions have ever appeared on his feet. At present all the finger nails have been destroyed and all the nail beds are inflamed, showing redness, edema and some exudation. The fingers show limitation of movement, apparently amounting to ankylosis of the second interphalangeal joints. The fingers also show considerable atrophy, apparently from disuse. Examination for fungi was unsuccessful.

DISCUSSION

DR. MAX SCHEER: I thought the lesion with the undermined border on the left palm was typical of acrodermatitis continua or dermatitis repens of Crocker, which I believe are the same.

DR. FRED WISE: The diagnosis as presented fits in with Hallopeau's disease, as far as one can tell now. It is by no means a classic example, because the patient has lesions scattered elsewhere, which does not fit in with Hallopeau's acrodermatitis, implying dermatitis of the extremities.

DR. LLOYD H. KEST (by invitation): I should like to suggest the possibility of arthropathic psoriasis. Some of the lesions on the hand, especially on the thenar eminence of the right palm, look typical of psoriatic lesions. The ankylosis present here would fit in with the diagnosis of arthropathic psoriasis.

DR. JACK WOLF: In acrodermatitis of Hallopeau and in pustular psoriasis one expects to see pustules. In the case presented tonight, I did not see any pustular lesions. I wonder whether it falls into that category?

DR. E. WILLIAM ABRAMOWITZ: What type of arthritis is involved, atrophic or hypertrophic?

DR. FRED WISE: It might be either or both.

DR. E. WILLIAM ABRAMOWITZ: This man never had arthritis at all; he has a disuse anklylosis. From the appearance of the eruption of the nails and hand, it is the first real case of acrodermatitis that I have seen.

DR. GEORGE M. LEWIS: I think that it is correct to say that Hallopeau's disease typically involves one nail or one nail bed. It seems to me that the history of injury in this case is important. There was increasing involvement of the nails until all were affected; hence the disease was progressive rather than symmetric. If Dr. Abramowitz will come to Welfare Hospital, I will show him atrophic arthritis with psoriasis. I think that the internists see more patients with atrophic arthritis and the dermatologists more with hypertrophic, because the latter are ambulatory.

CHICAGO DERMATOLOGICAL SOCIETY

MICHAEL H. EBERT, M.D., *President*

MARCUS R. CARO, M.D., *Secretary*

Jan. 19, 1944

Pituitary Basophilism (Cushing's Syndrome). Presented by DR. EDWARD A. OLIVER and (by invitation) DR. SAMUEL M. BLUEFARB.

I. S., a white woman aged 26, is presented through the courtesy of Dr. Arthur E. Mahle, of the Medical Department of Northwestern University. Her complaints on admission were amenorrhea of one and one-half years' duration, flushing of the face and dizzy spells.

About one year ago she was told that she had high blood pressure and diabetes. She had at that time polyuria, polydipsia and polyphagia, edema of the ankles and a tendency to bruise (ecchymoses) easily. An increase in weight became evident, from 150 to 250 pounds (68 to 113.5 Kg.), and with this increase in weight the presence of striae became noticeable. At present her weight is 200 pounds (90.7 Kg.).

At present the skin shows a lack of elasticity. Striae are noted on the anterior part of the shoulders, abdomen, thighs and back. Ecchymoses are present, and the skin in some areas is flabby. Perspiration is profuse in the axillas and on the palms. There has been an increase in the amount of hair on the face and body, although on the scalp the hair has become thin. The heart and lungs are essentially normal, and the blood pressure is 186 systolic and 130 diastolic. The patient presents all the features of Cushing's syndrome, namely, obesity, amenorrhea, weakness, high blood pressure, albuminuria, striae, ecchymoses and hypertrichosis of the face and trunk.

The urinalysis showed a 4 plus reaction for albumin but no sugar. The Kahn reaction was negative. The examination of the blood revealed 4,820,000 erythrocytes, 13,750 leukocytes with a normal differential distribution, and 15.2 Gm. of hemoglobin.

The treatment to date has consisted of sixteen weekly roentgen ray treatments of 200 r each to the pituitary gland.

DISCUSSION

DR. S. ROTHMAN (by invitation): A patient in the hospital with which I am associated displays the same fully developed picture of Cushing's syndrome as this patient does. But in addition to the striae she has loose atrophic spots on the elbows and knees, strikingly similar to lesions of acrodermatitis atrophicans. This combination makes me think of the possibility that the fragility of elastic fibers in acrodermatitis atrophicans is also of pituitary origin, acrodermatitis being overwhelmingly a disease of the menopausal age.

DR. MAURICE OPPENHEIM (by invitation): Concerning striae distensae (or atrophicae), which are so significant here, I want to direct attention to my investigations in cases of dermatitis atrophicans combined with striae. It is known that striae distensae are found in puberty, in adipositas and in severe generalized infectious diseases, for instance after typhoid. Striae are also found in pregnancy and after abortion at three months, but their absence is noted at times in spite of many pregnancies. One knows that dystrophic disturbances cause striae. My theory of the various types of striae distensae and of the various forms of dermatitis atrophicans is that they are on a congenital basis, due to a congenital or embryonal weakness of the elastic fibers, because in all these cases one finds absence of elastic fibers or finds the fibers torn so that they cannot be stained. The resistance of the elastic fibers is decreased, in some rare cases because of glandular disturbances (puberty, pregnancy) and in other cases because of tension, where the border of elasticity is reached earlier than in normal skin (acrodermatitis atrophicans, extensor area of knee and elbow joints, striae adolescentium). The connective tissue, which must be separated from the elastic tissue does not suffer in the beginning, but later after the loss of the elastic fibers which form the skeleton of the connective tissue, it degenerates too.

DR. E. M. SMITH JR.: I do not know whether the history mentioned this, but the patient has recently lost 50 pounds (22.7 Kg.) in weight in a little while. The roentgenographic examination showed an abnormality of the pituitary gland.

DR. M. H. EBERT: I have been interested in the etiology of striae for some time. In 1934 I reported 2 cases of striae distensae of a peculiar hypertrophic type in young women with other evidences of endocrine disturbance (ARCH. DERMAT. & SYPH. **31**:146 [Jan.] 1935). While under observation the raised, bluish borders became transformed into pale atrophic striae of the usual type. I am of the opinion that in a case like this, of Cushing's syndrome, there is not simply a mechanical tearing of normal elastic tissue. I believe the elastic tissue has been injured by some toxic substance, which results in its fragmentation. In pregnancy and in certain types of endocrine imbalance observed in adolescent girls a similar process is involved.

A Case for Diagnosis (Leukemia? Sarcoidosis?). Presented by DR. CLARK W. FINNERUD and (by invitation) DR. CLARK F. JOHNSON.

MRS. R. G., a farmer's wife aged 37, was admitted to the Presbyterian Hospital on Jan. 15, 1944. Her complaints were "elbow trouble" since 1939, pain in the stomach since January 1944, diarrhea since Jan. 8, 1944, and temperatures of 100 to 101 F. in the afternoons since Oct. 15, 1943.

In September 1935 the patient noticed that she had some small blisters on the inner side of her lower lip. She thought little of this, as she had had them periodically most of her life and they would just disappear. On this occasion the blisters broke and small ulcers formed on her lip, new blisters arose on the gums and tongue and these in turn broke down and small ulcerated areas resulted. This cycle kept up for some time. The patient went to the Central Free Dispensary in January 1936 for treatment of the sores in the mouth, and at this time she had four or five lesions on the breast resembling the lesions that she now has on her back. Biopsy was performed on these by Dr. Scull, and then they were treated with roentgen rays. They promptly disappeared.

She went to the Mayo Clinic in June 1937, seeking relief from the oral sores. A complete study was made there, and a lesion resembling those found on the breast was discovered on the left shoulder. This was elliptic, indurated, raised and reddish. Diet, gargles and various other medicaments, such as vitamins, had no effect on the oral lesions.

In October 1940 a small tumor was removed from the cervix of the uterus, and thereafter there was a constant flow until Nov. 20, 1940, when a hysterectomy and oophorectomy were performed by Dr. E. S. Denney at the Copley Hospital, Aurora, Ill. The patient was told that her ovaries and uterus were "diseased." She had no sores in the mouth after this operation,

and she attributes the cure to the surgical procedures. She states that a maternal aunt underwent a similar experience.

In November 1939 the patient felt a mass on the lateral aspect of her right elbow, approximately 1 cm. in diameter. This was removed under local anesthesia, and she was told that it was a "fatty tumor." The healing was slow, and there developed a raised, hard mass that encircled the operative site; this was removed in January 1942, as it was causing considerable pain. There was another similar mass as big as a hen's egg on the medial aspect of the elbow. In September 1943 this mass was removed, and the incision has never healed completely. At this time she was told that there was a similar mass above the lateral aspect of the elbow about 10 cm. above the original mass, but this has not been excised. In September 1943 she also noticed a hard indurated mass involving the medial side of the left eyebrow and upper lid and also a hard raised mass that can now be seen just below and lateral to the left eye. This has itched a great deal and at first increased in size but has become smaller in the last five weeks. Similar lesions, which are circular, raised, reddened and pruritic, have appeared periodically on the back of the chest, arms and legs. They vary in size and shape from day to day, getting larger and smaller at times, but they persist. Some "small pimples" developed on the abdomen, chest, back, neck and arms on Dec. 21, 1943. These also persist.

The glandular enlargement was noted first five years ago on the right side of the neck and this has progressed now to a generalized lymphadenopathy, but the enlarged glands on the left side of the neck were not noticed until Jan. 2, 1944. These have become large, ache at the end of the day and pain more if they are scratched or rubbed. The large gland in the right inguinal region was first noted one week after the hysterectomy.

On examination of the skin there is a pinpoint-sized papular rash on the abdomen, chest, back, neck and arms. On the back, arms, legs and shoulders may be found the raised, indurated, coin-shaped, reddened areas from which a specimen for biopsy has been taken. Hyperkeratosis is noted on the surface of some of these lesions. To palpation they feel as if they penetrate deeply into the subcutaneous tissue. In the region of the right elbow and cubital space, scars can be seen where walnut-sized to egg-sized masses have been removed, as previously described. On the medial aspect of the elbow can be seen the poorly healed area, which is raised and indurated. There is a definite hypertrophy of the supraclavicular nodes on the left side. These are hard, multilobular and only slightly tender. They do not appear matted to the surrounding tissues or skin. The posterior auricular nodes on both sides are hypertrophied, and those in the anterior triangle of the neck on the right side are similarly hypertrophied. There is a single palpable node, of the size of a peanut, in each axilla, which is hard, movable and slightly tender. In the groins there is bilateral hypertrophy of the nodes, and deeper the smaller nodes can be felt.

On examination of the chest the excursions are greater on the right, with seemingly depressed activity on the entire left side of the chest. The pulmonary fields are clear to percussion and auscultation. The heart appears to be normal. There is pronounced tenderness with spasticity over the entire abdomen, especially over the upper left quadrant. There is a scar on the midline in the lower portion, with apparently good healing. The spleen is enlarged. The liver is enlarged, dropping approximately 3 fingerbreadths on inspiration.

Laboratory Data.—The examination of the blood showed 4,100,000 erythrocytes, 12 Gm. of hemoglobin and 12,000 leukocytes, with 82 per cent eosinophils (adult cells), 11 per cent polymorphonuclears (adult cells), 6 per cent lymphocytes and 2 per cent mononuclears. The urine was normal except for a trace of albumin.

The agglutination titers of the blood were 1:20, 1:40, 1:80 and 1:120. There were no agglutinations with Eberthella typhi O, Eberthella typhi H., Salmonella paratyphi A, Salmonella paratyphi B., Proteus OX 19 and Brucella abortus.

Fluoroscopic examination of the chest showed nothing abnormal except for a healed Ghon lesion on the left in the fourth interspace; the colon was normal; the stomach was normal, but there was a mass in the epigastrium which was anterior and extrinsic to the stomach.

The temperature was 100 F. on admission but has been normal since.

DISCUSSION

DR. H. E. MICHELSON, Minneapolis: Since this patient has been so thoroughly studied and no definite diagnosis arrived at, the only suggestion that I can make is that the enlarged lymph nodes in the neck and the microscopic picture somewhat suggest Hodgkin's disease.

DR. PAUL A. O'LEARY, Rochester, Minn.: I saw this patient approximately five years ago, when she presented only one lesion on the shoulder and some lesions in the mouth. The examination of the tissue removed at that time was indeterminate. Today I favor a diagnosis of leukemia cutis, believing the exact type will be determined when a more typical blood picture eventually develops.

DR. R. H. SCULL: I first saw this patient in 1937, in the department of allergy, at which time she complained of multiple recurring ulcers of the mouth and tongue. She later complained of some bluish red macular lesions of the right breast as a result of a child's pinching the breast while nursing. The slide presented today is a section of a biopsy specimen taken at that time. The physical and laboratory examinations, including blood tests and a blood count, showed nothing significant. I later saw her with two or more lesions of the same description on the back that came without the history of trauma.

DR. LOUIS BRUNSTING, Rochester, Minn.: The high percentage of eosinophils is of particular interest. It recalls a case in my experience, that of an elderly man who presented a chronic bullous eruption like erythema multiforme or dermatitis herpetiformis with pigmentation. The values for red and white blood cells were normal, but the percentage of eosinophils ranged well over 60 per cent. There were no immature forms, but within a period of less than a year the patient died, and shortly before death the white cell count total exceeded 200,000 per cubic millimeter. In the early stages these odd forms of lymphoblastoma are often not sufficiently differentiated to be identified.

DR. UDO J. WILE, Ann Arbor, Mich.: May I ask the presenters whether the enlargement of the lymph glands and the blood picture antedated the eruption?

DR. C. W. FINNERUD: According to the history—and I have not all the points of the history clearly in mind, as I saw the patient for the first time night before last—the glandular enlargement preceded the appearance

of the cutaneous lesions. I saw the sections for the first time when they were brought over this afternoon. From the specimen that was taken yesterday afternoon from the shoulder it is evident that the disease is not sarcoid. When I saw her in consultation because of these plaques on the elbow, several on the back and over the left zygoma and the generalized lymphadenopathy plus the rather huge spleen and enlarged liver, I thought of the possibility of Schaumann's disease, but the chest and also the phalanges have been examined roentgenographically and there were no noteworthy changes there. I think eventually we shall find it is leukemia. As mentioned, the leukocyte count now is only 12,000. The differential count with 82 per cent eosinophils is particularly interesting. I could not see enough resemblance to Hodgkin's disease, at least in the sections, to warrant that diagnosis. Here again the eosinophil count is interesting. My feeling is that it will turn out to be leukemia.

Pemphigus Vulgaris. Presented by DR. DAVID V. OMENS and (by invitation) DR. HAROLD D. OMENS and DR. M. OTSUKA.

Mrs. A. P., a Czech housewife aged 67, presents a generalized infiltrated inflammatory eruption of the skin on which are numerous variable-sized bullae, some of which contain clear fluid while others are lactescent; itching and burning sensations are present more or less constantly. The eruption has been present for about seven weeks, starting on the back about the scapular areas.

The Wassermann and Kahn reactions were negative. The urine was normal. Examination of the blood showed 60 per cent hemoglobin, 3,520,000 erythrocytes and 12,000 leukocytes.

The examination of a specimen removed at biopsy revealed the bullae to be unilocular and formed by the separation of the epidermis from the cutis. The blister contained fibrin and leukocytes, the majority of which were eosinophils. The papillae which formed the floor of the bullae were enlarged as a result of edema. The blood vessels in the deeper portion of the cutis were dilated and contained blood cells.

DISCUSSION

DR. RUBEN NOMLAND, Iowa City: I am inclined to believe that this patient has pemphigus, but I am not absolutely certain. I wish, however, to make a report on some rather interesting features that have been noted in the last 5 or 6 cases of pemphigus that I have seen, that is, disturbances of the blood proteins. In 5 patients so far examined there has been almost always a decrease in the amount of protein in the blood, and almost always associated with this decrease there is an inversion of the albumin-globulin ratio, the globulin fraction being greater than the albumin. As nearly as I can tell from the limited number of patients studied, the greater the disturbance of the protein in pemphigus the more serious the prognosis. Unfortunately I have not had opportunity to check on other bullous disturbances to see whether they likewise are accompanied with disturbances of serum protein.

DR. UDO J. WILE, Ann Arbor, Mich.: Probably all dermatologists feel that time is the thing that establishes the diagnosis of pemphigus in so many cases in which in the beginning it is difficult to make a differential diagnosis. This case, notwithstanding this woman's age, the extent of the eruption in seven weeks, the pronounced erythema and the configuration of some of the lesions in annular form, impresses me more at the moment as one of a bullous erythema. I think that all dermatologists, however, have at times made the diagnosis of dermatitis herpetiformis and of erythema multiforme, only later to find pemphigus developing.

DR. THEODORE CORNBLEET: I am inclined to agree with Dr. Wile's diagnosis. The grouping of lesions, together with the excessive itching and erythema, points rather to erythema multiforme or dermatitis herpetiformis than to pemphigus. As is well known, the differential diagnosis among this bullous triad is often impossible early in the course of an eruption. There is a natural difference of opinion when such a picture is shown to a number of dematologists. This emphasizes the need for an additional differential aid.

For this purpose I attempted to measure and compare the amounts of protein in the blister fluid and blood serum. It was found that the blisters of pemphigus, unlike those of some other bullous diseases, contained relatively more protein than blisters of erythema multiforme or of Duhring's disease. If there are many blisters present, it is inevitable that an appreciable amount of protein is withdrawn from the blood. The albumin molecule being much smaller, it escapes from the blood into the blister easily while the globulin is held back more readily. Consequently there is a tendency for a reversal of the normal albumin-globulin ratio in pemphigus. A similar situation is present in nephrosis. This altered ratio of the serum proteins, I believe, is merely a depletion phenomenon and carries no causal implications. Unfortunately, therefore, I believe it is useless to follow this lead in the hope of learning the cause of the disease.

DR. FREDERICK R. SCHMIDT: About fifteen years ago Dr. William F. Peterson and I studied these bullous eruptions. We found increased permeability in all bullous diseases, not only in pemphigus. We came to the conclusion that in addition to this there is also a constant alteration of the albumin-globulin ratio. But there was one factor that differentiated pemphigus from the other bullous diseases, and that was that the color index in pemphigus approached or exceeded 1. In the case of the woman seen this afternoon the earliest color index was exactly 1; in the second count it was over 1. I have noticed that in fatal and progressive cases the color index is constantly over 1.

DR. M. H. EBERT: I think that every attempt to find some criteria whereby one can distinguish fatal pemphigus from the more or less benign bullous eruptions, dermatitis herpetiformis and bullous erythema multiforme, is valuable. From clinical observation I should say that this is a case of dermatitis herpetiformis. It has all the features. There is the eosinophilia, both in the blood and in the bullous fluid; there are the characteristic itching, the edematous wheals, and the absence of lesions in the mouth. On the other hand, my clinical experience is that in cases of this type I am afraid the disease will eventuate fatally, so whether one calls it dermatitis herpetiformis or dermatitis multiforme or pemphigus makes little difference.

A Case for Diagnosis (Heavy Metal Dermatitis?). Presented by DR. THEODORE CORNBLEET and (by invitation) DR. H. C. SCHORR.

R. A., a Negro woman aged 32, has had an eruption since June 1943, which began on the forearms and about the waistline and was dry. It cleared during the application of an ointment. After this she was given twelve injections each in an arm and hip, though

the result of her blood test was said to be satisfactory. An eruption appeared which was scaly and not pruritic. It is not clear from the history that it followed immediately after an injection. Six more injections were given, and the patient said that these made the rash worse. Then the scaling gradually subsided, and it has remained in its present state for several months. It is the patient's opinion that the present conspicuous lesions resulted from the injections she received.

The less conspicuous changes in the skin on the extensor surfaces of the forearms and face appeared in October 1943, for which the patient was hospitalized for four weeks. The lesions were exudative and covered with crusts, and their character differed entirely from the earlier and drier ones. The moist eruption has greatly improved, to leave faint residues.

Now there are patches and plaques which coalesce to form sheets, especially over the upper part of the thorax. These are sharply outlined and scalloped in some places. There are lichenoid insets which show more scaling than the rest. All the lesions are fairly superficial. The pigmented areas have scattered through them other areas which are depigmented and sharply defined. On the extensor surfaces of the forearms and on the lower parts of the arms and on the face and neck is a faint erythematous dermatitis, slightly scaly and edematous in places and poorly outlined. The small amount of pigmentation at the latter sites contrasts with that present at the others. There is little itching. The gums and mucosae of the mouth have a normal appearance. There are moderately enlarged cervical lymph nodes, but the other accessible chains are not enlarged.

Sections of a biopsy specimen taken at a pigmented site were examined by the dark field method, but the appearance was not suggestive of a heavy metal as the etiologic factor.

Laboratory studies of the urine and blood while the patient was in the hospital recently showed nothing abnormal.

DISCUSSION

DR. CLEVELAND WHITE: The appearance is suggestive of a possible contact dermatitis, but there is no history of her working with powder. I think the diagnosis as presented will turn out to be the correct one.

DR. F. W. LYNCH, St. Paul: The discrete nature of the papules, the hyperpigmentation and the distribution on the medial aspects of the thighs and flexor surfaces of the upper extremities point to a diagnosis of lichen planus. The microscopic picture is compatible with that diagnosis and does not show any particular evidence of toxic changes due to heavy metals. Since the patient is unable to give a satisfactory history as to the exposure to metals and the onset of the eruption, I prefer the diagnosis of lichen planus to that of a toxic eruption resembling that disease.

DR. HERBERT RATTNER: I agree with Dr. Lynch. Most of the lesions in this case strongly suggested lichen planus. Others simulated pityriasis rosea. They were all rather more deep seated than are lesions of these diseases usually; and they could well be manifestations of a drug eruption, perhaps of the biotropic type.

DR. MAURICE OPPENHEIM (by invitation): I agree with the diagnosis of Dr. Lynch and Dr. Rattner. I am not very familiar with diseases of the skin of Negroes, but if the same picture were present in a white person I would think of lichen planus atrophicus pigmentosus. The histologic picture does not speak against it. It may be influenced by the injections, which contributed to the pigmentations.

DR. THEODORE CORNBLEET: There were many lichenoid lesions, but none that I felt were typical of lichen planus. The histologic changes, too, were in my opinion not confirmatory for this diagnosis. The history suggested that this was a lichenoid eruption following the administration of a heavy metal. Dark field examination of sections of tissue from the lesions, however, did not show any of the usual heavy metals to be present. I am uncertain whether this negative finding excludes the possibility that a heavy metal has caused these lesions.

Convex Finger Nails and Toe Nails with Nutritional Anemia. Presented by DR. EDWARD A. OLIVER and (by invitation) DR. SAMUEL M. BLUEFARB.

M. B., a white woman aged 22, presented herself for treatment of the peculiar formation of the nails of the fingers and toes. They present a convex surface, both longitudinally and transversely, the opposite of koilonychia and reminding one of club fingers. They differ from club fingers in that the pulps of the fingers are not distended and the phalanges taper normally. The nails are thicker than normal and have lost their luster. The nails of the thumbs and index fingers have been lost in the past, and the new nails coming in have assumed the formation of the previous nails.

At the age of 6 she had asthma and was found to be allergic to feathers, milk, rice and potatoes. At present she has no asthmatic symptoms. At the age of 11 she had lobar pneumonia.

The blood pressure was 108 systolic and 70 diastolic. The heart and lungs were essentially normal. The basal metabolic rate was +7 per cent. The urinalysis showed normal values. The Kahn reaction was negative. The hematologic examination showed 4,000,000 erythrocytes, 9,500 leukocytes with a normal differential distribution and 50 per cent hemoglobin.

DISCUSSION

DR. ARTHUR C. CURTIS, Ann Arbor, Mich.: The type of nails presented by this patient was not the usual type seen in idiopathic microcytic anemia. Because the changes in the nails are of ten years' duration, they may be a manifestation of some type of congenital dystrophy.

DR. S. M. BLUEFARB (by invitation): While it is true that in anemia one usually observes a spoon-shaped nail (koilonychia), there was a reference recently in *The Journal of the American Medical Association* to this type of nail with this type of anemia. A complete physical examination was made, and the only significant observations were the 50 per cent hemoglobin content and the low red blood cell count. It is our intention to give her liver and iron and to see what, if any, change can be observed in the nails.

Dermatitis Repens. Presented by DR. E. A. OLIVER and (by invitation) DR. H. H. RODIN.

N. H., a white woman aged 41, who resided on a farm in Tennessee until one month ago, was admitted to the dermatologic clinic, Northwestern University, on Jan. 4, 1944. She complained of an eruption confined to the right thumb and right foot of nine months' duration.

The lesion began on the tip of the right thumb shortly after the part had been injured by a stem of a cotton plant and punctured by a needle, both events occurring on the same day and in the same area. One week later a similar lesion appeared on the lateral arch of the

right foot. She then had an attack of malaria followed by a more rapid spread of the existing eruption.

The past history contains nothing significant except that she had been treated for symptoms of menopause during the last year.

The examination reveals an acute inflammatory dermatosis confined to the right thumb and the lateral arch of the right foot containing numerous intraepidermal abscesses with undermining of the epidermis at the edges.

Treatment has consisted solely of local applications of 5 per cent sulfathiazole ointment.

DISCUSSION

DR. UDO J. WILE, Ann Arbor, Mich.: This did not look like dermatitis repens to me. It had a striking resemblance to a late syphilid. I wonder whether the patient has been investigated with regard to the presence of latent syphilis. The lesion on the sole had an atrophic scar and was entirely painless.

DR. F. E. SENEAR: I had much the same feeling with regard to the possibility of dermatitis repens. It seemed to me that the central portion of the lesion on the foot, where healing had taken place, leaving a thin atrophic scar and no semblance of any activity such as is usually seen in dermatitis repens, would argue against that diagnosis. Also I felt that the lesion on the hand was made up of individual nodules in one part of the circumference. There were four or five individual nodules in one place.

DR. M. H. EBERT: How long has the eruption been going on?

DR. H. H. RODIN: Eight or nine months.

DR. EDWARD A. OLIVER: The picture today is distinctly different from what it was when we saw the patient two weeks ago. There was considerably more infection present then. She was given a sulfathiazole ointment, and the eruption has improved greatly with that therapy. I, too, think that there is some question about this being dermatitis repens. The case should not have been presented with that diagnosis.

Exfoliative Dermatitis (Psoriasis). Presented by DR. DAVID V. OMENS and (by invitation) DR. M. OTSUKA and DR. HAROLD D. OMENS.

B. A., a widowed Negress aged 52, a laundry worker, presents a generalized erythroderma, scarring of the medial aspect of the left leg and a bluish macular pigmentation of the deltoid areas and the bends of both arms.

The erythroderma has been present for the past four months. It started after the use of a white salve prescribed by the city health department, which burned and smarted on each application. The patient has had psoriasis for the past twenty-five years with the usual seasonal exacerbations and remissions.

She was treated for syphilis for ten years, with no treatment for the past four years. She also had been a morphine addict for twenty-two years, but she gave up the habit ten years ago. The results of a urinalysis and a hematologic examination were normal. The Kahn reaction was negative. Examination of the section removed at biopsy showed parakeratosis of the stratum corneum, absence of the stratum granulosum, uniform acanthosis with intercellular edema and spongiosis, slight clubbing of the papillary body, with dilatation of the blood vessels, and a perivascular infiltration of lymphocytes in the subpapillary portion of the corium.

DISCUSSION

DR. HERBERT RATTNER: My information was that the exfoliative dermatitis had followed intravenous injections of some medicine. The exfoliative dermatitis cleared, and now there is visible the psoriasis.

DR. JAMES H. MITCHELL: Psoriasis in a Negro is sufficiently rare to call itself to any one's attention. I talked to this woman today, and she recalled that I had taken a colored picture of her fifteen years ago. About two years ago I took another. I have here the original picture which showed a typical psoriasis on the knees and chin and no sign of exfoliative dermatitis at that time.

DR. R. H. SCULL: I first saw this patient some years ago at Provident Hospital. The diagnosis of psoriasis was made and a photograph was taken at Rush Medical College. The lesions then were classic both in appearance and in distribution. I recall that when I brought her to the hospital for a biopsy some of the blue areas were typical of a morphine addict.

DR. DAVID V. OMENS: This patient has had psoriasis for twenty-five years, she gives a history of having spent some time in jail. She has had no treatment for syphilis for the past four years, and she makes no mention of taking internal medicine of any kind. She was treated for psoriasis by the city board of health with applications of sulfur. She says that two or three times when she applied salve to the skin it became red with this generalized erythema.

Psoriasis. Presented by DR. DAVID V. OMENS and (by invitation) DR. HAROLD D. OMENS.

J. S., an American married man, a bookkeeper, presents an eruption involving both hands, especially the fingers, on the palmar and dorsal surfaces. The eruption is composed of variable-sized papular lesions, definitely infiltrated, with a tendency to coalesce to form patches and covered with flaky scales. There is evidence of similar lesions on both elbows. On the hands there are fissures associated with the lesions which are painful and interfere with his occupation.

DISCUSSION

DR. S. W. BECKER: In the absence of positive biopsy evidence I could hardly make a diagnosis of psoriasis. The lesion on the right elbow I thought was a little too low for a psoriatic lesion and was probably a neurodermatitis. The lesions on the palmar surface of the fingers resemble linear keratosis. The eruption is unique, but I do not believe that it is psoriasis.

DR. MINNIE O. PERLSTEIN: To me this does not resemble clinical psoriasis. It resembles the lesions which we have been calling keratoderma climactericum. Men with this picture respond to endocrine therapy as do women. The picture this patient presents and the linear lesions on the tips of the fingers are usually seen at the onset. They progress and become a generalized keratoderma. The tips of the fingers become sensitive. I have a group of 4 women and 2 men whom I have been treating for the past three months with an ointment containing diethylstilbestrol. They are improving. In addition to the local therapy, I have been using testosterone propionate for the men and for the women diethylstilbestrol by mouth. When the endocrine therapy is discontinued, a relapse occurs which is controlled by resumption of endocrine treatment.

DR. M. R. CARO: I agree with the diagnosis of psoriasis in this case. Several years ago we had

a patient at the University of Illinois with lesions on the knuckles which resembled the lesions here except that they were more shiny. A biopsy was performed and it showed the typical histologic picture of psoriasis. A few months later characteristic lesions of psoriasis developed on the elbow, further confirming the diagnosis. Since that time we have seen a considerable number of patients with identical lesions on the knuckles, for whom we made the diagnosis of psoriasis. It is my impression that when it is limited to this location psoriasis is generally mistaken for other dermatoses, especially neurodermatitis. Lesions of psoriasis on the knuckles are resistant to treatment.

Kaposi's Sarcoma. Presented by DR. HERBERT RATTNER and DR. MAURICE DORNE.

J. C., a white man aged 74, presents an eruption on the feet and hands which first appeared about three months ago. There is a violaceous thickened patch covering each foot to the ankle in a "socklike" manner. There is a papule the size of a split pea on the left palm and a number of flat pea-sized papules on the ulnar side of the dorsal surface of each hand. There is no adenopathy.

Examination of the urine and blood gave essentially normal results. Histologic examination of a section taken from the foot showed the features of Kaposi's sarcoma.

DISCUSSION

DR. NORMAN TOBIAS, St. Louis (by invitation): The diagnosis appears to be Kaposi's sarcoma. I do not think that the lesions are benign, as the unusual conformation suggests invasion along the lymphatics.

DR. MAURICE DORNE: We saw this patient several days ago, and we did not hesitate to make a clinical diagnosis of Kaposi's sarcoma. We were much impressed with the "socklike" distribution of the eruption and the rapidity with which it developed; if the history is correct, it is of only three months' duration.

Blastomycosis. Presented by DR. OLIVER S. ORMSBY.

W. A. L., a man aged 49, has had an eruption for five years. It began as a boil-like lesion on the right forearm. This spread peripherally, and new lesions developed in other situations. New lesions have developed recently on the lip and nose. At the present time there are lesions on the right forearm and elbow which present a thin cigaret-paper-like scar in the center while the upper and lower margins are crust covered and ulcerated. Similar lesions are present on the abdomen. There is a large fungating lesion on the lower lip and beside the nose. The patient has lost 40 pounds (18.1 Kg.) in weight. The treatment in the past, both local and internal, has had little effect. The activity of the disease has been reduced about four fifths in six weeks' treatment. This consisted of four injections of arsphenamine and the internal use of potassium iodide together with a combination of vitamins.

DISCUSSION

DR. E. M. SMITH JR.: I have tried sulfadiazine in my 1 case of blastomycosis, and it seems to have better effect than potassium iodide. I have been trying to get some penicillin for use in a case of blastomycosis but have been unable to obtain any. There was a patient in one of the hospitals who was getting 500,000 units; so we have collected the urine, and an attempt will be made to extract it. About 85 per cent of the penicillin secreted in the first twenty-four hours can be recovered.

DR. OLIVER S. ORMSBY: It seems rather superfluous to discuss blastomycosis at this time. I have heard from physicians all over the country who have treated blastomycosis with potassium iodide and also copper sulfate without much success. It was many years ago that I instituted treatment with arsphenamine. My colleagues and I would use potassium iodide until it ceased to be effective, when its use would be temporarily suspended. We would then give a series of three to five injections of arsphenamine, and then resume the administration of potassium iodide. In a comparatively short time good results were obtained. I am sure that this method of treatment is valuable and one that should be emphasized. The patient shown today illustrates this fact.

Within a few years Martin and Smith (Martin, D. S., and Smith, D. T.: Blastomycosis [American Blastomycosis, Gilchrist's Disease]: I. A Review of the Literature, *Am. Rev. Tuberc.* **39**:275 [March] 1939; II. A Report on 13 New Cases, ibid. **39**:488 [April] 1939) concluded that patients resistant to potassium iodide are allergic. They proposed the use of a vaccine made from blastomycetes to reduce the hypersensitiveness and then use of potassium iodide. They got the same results by this method that we do with the arsphenamine and potassium iodide.

In the eight weeks we have been treating this patient, we used potassium iodide for one month and then gave four injections of arsphenamine and then returned to the use of potassium iodide. He has now had 80 per cent clearing, and I look for him to have entire clearing within a reasonably short time.

Actinomycosis. Presented by DR. E. A. OLIVER and (by invitation) DR. ARTHUR GREENBERG.

The patient, a Negro man aged 48 years, states that four months ago he struck his lower left side against the edge of a chair. The swelling appeared one week later and was rather painful. He states that the swelling has been lanced several times by his physician but that at times pus is discharged spontaneously. He has lost 19 pounds (8.6 Kg.) since October 1943 but complains of no cough, night sweats or hemoptysis.

The examination discloses a palm-sized brownish area on the left side of the chest. There are several discharging sinuses in this indurated plaque. He also has a nodule on the back of the neck and a firm cystic mass on the lower third of the right thigh. This lesion is about the size of a small plum. Actinomycetes were found in the discharging sinuses in the lesion on the abdominal wall.

DISCUSSION

DR. UDO J. WILE, Ann Arbor, Mich.: I think that there were some features of this case which did not fit in altogether with the usual case of actinomycosis. In the first place, actinomycosis usually involves bone. In the second place, two lesions in actinomycosis occurring at such widely separated points are also somewhat unusual. The fact that ray fungi may have been found in the discharge is of importance only if they are consistently found. It would have to be confirmed by more than a single examination. The patches he had on his thigh and foot are a great deal like cold abscesses. Tuberculosis of a rib or of the pleura could well go with the type of lesion he had in his chest. I think that before one accepts the clinical diagnosis of actinomycosis the case should be studied a little further, with regard to study for tuberculosis and also supplemented by a biopsy.

DR. E. A. OLIVER: The roentgenogram showed definite changes in the left side of the chest.

DR. PAUL A. O'LEARY, Rochester, Minn.: Penicillin has been used successfully in the treatment of actinomycosis of both the cutaneous and the visceral types. The dose given approximates 500,000 Oxford units, and the less surgical intervention there has been the more satisfactory is the response.

DR. E. A. OLIVER: I did not see the actinomycetes, but there is a good pathologist at the Veterans Hospital, who told me he has found actinomycetes on several occasions. I saw the patient thirteen days ago, and I thought that his disease was sufficiently interesting to bring him to this meeting. It has been a rather acutely developing case. The man has lived in Chicago all of his life. He worked for several years as a houseman. More recently he had been employed by the Campbell Soup Company. The lesions on the neck have just recently developed. The roentgenogram of the chest shows considerable infiltration in the left lung. The disease has developed so rapidly that I think one might well question the diagnosis. He has had some fever. I feel positive, however, that this is a definite case of actinomycosis.

Multiple Hemangiomas. Presented by DR. E. A. OLIVER and (by invitation) DR. ARTHUR GREENBERG.

The patient, a white man aged 52, states that he first noticed little wartlike lesions on the third finger of the right hand about four years ago. These lesions were diagnosed as warts and were cauterized. About six months later similar spots appeared on the right arm and in the region of the left elbow. These were also cauterized with acids. Shortly thereafter the lesions on the hands appeared. About two years ago the lesions on the soles of his feet appeared.

The symptoms are pruritus, worse at night, and bleeding when the lesions are slightly injured.

The Kahn reaction was negative. The blood count and urinalysis were normal. A biopsy from a lesion on the hand was made and was diagnosed by the pathologist at the Hines Veterans Administration Facility as multiple hemangiomas. There are thickened, reddish blue patches of irregular sizes and shapes on both palms, the plantar aspect of the feet, including the toes, and the lateral aspect of the right arm.

DISCUSSION

DR. C. W. LANE, St. Louis: Unfortunately, I did not have a chance to see the section, and so my impression is purely a clinical one. The violaceous color of all the lesions, the warty excrescences on the surfaces of many of them and the history of their occurrences in areas of trauma, e. g. the biopsy site and burns, were indicative to me of Kaposi's sarcoma.

DR. S. W. BECKER: I should like to call attention to the fact that Kaposi's sarcoma per se is not a malignant tumor. It may become malignant later and eventuate in sarcoma, but ordinarily it should not be classed as a malignant tumor. Clinically I thought that this man presented Kaposi's sarcoma, but the sections showed a large number of endothelial cells around spaces filled with red blood cells. I believe that in consideration of the clinical picture a diagnosis of Kaposi's sarcoma could be made from the sections.

DR. EDWARD A. OLIVER: I saw this man about three weeks ago and made a diagnosis of Kaposi's sarcoma. The histologic report was multiple hemangiomas. I could not correlate the clinical picture and the development later in life with this diagnosis. To me it was Kaposi's sarcoma.

A Case for Diagnosis (Kaposi's Sarcoma?). Presented by DR. E. A. OLIVER.

A year and a half ago, while the patient was in the Army, an ulcer developed on the left leg shortly after he had struck it on the tail of an airplane. Later three other ulcers developed on this leg and have persisted without healing. In addition, he noticed a small ulcer on his scalp; it was excised and has healed. There has been only a slight loss in weight.

The examination reveals a fairly well developed, fairly well nourished white man of 23, not appearing acutely ill. The head and neck are normal except for a healed scar on the scalp. The heart and lungs reveal no abnormality. The liver, spleen and kidneys are not palpable. There are numerous large ulcerations on the left leg. On the left thigh there are several purplish subcutaneous nodules, firm in consistency. The ulcerations on the leg are rather deep, involving the muscles, covered with a necrotic material, and of ragged outline.

The roentgenograms of the chest revealed no abnormality. The cultures of the material from the ulcers revealed many gram-negative bacilli but no fungi. Examination of the biopsy specimen from the ulcers revealed multiple hemorrhagic sarcoma.

The blood count was within normal limits. The urinalysis revealed a faint trace of albumin. The Kahn reaction was negative.

DISCUSSION

DR. H. E. MICHAELSON, Minneapolis: I saw this patient after he had been in a military hospital for about a year. He had first been treated for pyoderma and ringworm, but later microscopic sections were diagnosed as Kaposi's sarcoma. Since there was such decided ulceration and the lesions clinically did not strike me as Kaposi's sarcoma, I had him go to Rochester, and Dr. O'Leary was greatly surprised when the section that they made also suggested the diagnosis of hemorrhagic sarcoma. Since then the patient has had some metastases to the scalp, and I believe that his general condition has not changed much. Evidently the diagnosis is some form of sarcomatous malignant neoplasm, but it is hard to arrive at a final decision.

It must be remembered that "malignancy" is a clinical term, and, regardless of what the microscopic picture is, what the disease does to the patient is what determines how malignant the condition is.

DR. PAUL A. O'LEARY, Rochester, Minn.: As Dr. Michaelson said, this case is unique. When I first saw this patient the possibility of a Kaposi sarcoma seemed remote; and as the histologic sections he brought with him, taken in two Army hospitals, were inconsistent with the clinical picture we performed another biopsy. Dr. Montgomery favored a diagnosis of Kaposi's sarcoma, and the three general pathologists who examined the sections gave three different opinions, all tending, however, to favor a diagnosis of sarcoma of some sort.

Now that he has metastatic lesions of the scalp and from the numerous histopathologic studies that have been made, I favor a diagnosis of a hemangioendothelioma. An amputation was recommended some months ago but was refused by the patient, and now the process has gone too far for such a procedure.

DR. S. W. BECKER: I saw this section before I saw the patient. In view of the facts that spindle-shaped cells

extended deeply, more deeply than usual in Kaposi's sarcoma, and that there was an area of necrosis, which is not seen usually in Kaposi's sarcoma, I thought that the diagnosis should probably be spindle cell sarcoma. I think clinically also it is not Kaposi's sarcoma.

A Case for Diagnosis. Presented (by invitation) by DR. M. OPPENHEIM.

M. S., a white man aged 27, presents an eruption on both shoulders, partially on the neck, of red areas in ring form. These areas are 2 to 3 cm. wide and are limited by single or confluent superficial blisters. The blisters have a whitish content and the rings of blisters are bordered by halos of inflammatory redness. The central areas are covered with normal skin. There are no pigmentations or scars. The lesion on the right side of the neck is the size of a walnut and is elevated, with indistinct borders and central blisters. The lesions begin with small superficial blisters surrounded by an intense red halo with indistinct limits, like impetigo simplex.

The disease started in 1934 with blisters and mild itching on the right shoulder. The patient was treated at that time with compresses of solution of boric acid and boric acid ointment. When I saw him a year ago, the diagnosis of impetigo serpiginosa was made and sulfathiazole internally and externally was used. After the internal treatment with sulfathiazole, the lesions cleared completely, but in a short time the eruption recurred. Sulfathiazole ointment had no effect. Later the patient was treated with injections of oidiomycin, acetarsone and grenz rays without favorable results.

The Kahn reaction was negative. The urinalysis and blood count were normal. The smear of the blister fluid revealed intracellular and extracellular staphylococci.

DISCUSSION

DR. NORMAN TOBIAS, St. Louis: I had the impression that this was a case of Hailey and Hailey's type of benign pemphigus, based on the duration of ten years, the absence of constitutional symptoms, the frequent remissions and exacerbations, the localized nature of the patches, composed of crusted and bullous elements, and the resistance to treatment. Although there was no history of other cases in the family, I have seen 2 or 3 cases in which there was no hereditary history.

DR. M. H. EBERT: I am glad to hear Dr. Tobias make this statement. That was my clinical diagnosis.

DR. F. W. LYNCH, St. Paul: A few years ago I presented a patient with a similar eruption at a meeting of the Minnesota Dermatological Society. I regarded that case as one of the benign dyskeratotic bullous eruptions described by Hailey and Hailey as benign pemphigus. I believe that Dr. Oppenheim's patient has the same disease, even though the history of familial involvement is absent. In my patient, as in Dr. Oppenheim's, the eruption responded temporarily to the oral administration of sulfathiazole.

DR. S. W. BECKER: I think that is what Dr. Obermayer and I called dyskeratosis bullosa hereditaria. The human generations are so far apart that one neglects to find out whether a man's children acquire the disease. It usually comes on at 18 years of age. We have seen 2 or 3 instances in which there was only one member of a family involved, but it may be that their cases may be the beginning of the disease on a familial basis.

DR. THEODORE CORNBLEET: Because of the dyskeratosis that is present may I suggest that Dr. Oppenheim determine the vitamin A level of the blood and also perhaps administer this vitamin therapeutically?

DR. MICHAEL H. EBERT: What would be the basis?

DR. THEODORE CORNBLEET: The basis for this suggestion is the similarity of the fundamental histologic change, namely, dyskeratosis both in this patient's lesions and in keratosis follicularis. The similarity is so great that some investigators believe that benign familial pemphigus is a variant of Darier's disease. If the same therapy should be equally successful in the two diseases, this would not prove their identity. Thus a lack of dietary vitamin A may produce a keratosis of the follicles, and the same factor has been successfully employed in treatment of Devergie's disease. Both show the common denominator of keratosis of follicles and improvement from the use of vitamin A and yet are not identical.

DR. MAURICE OPPENHEIM (by invitation): I do not think that this is a case of familial pemphigus. It is also not epidermolysis bullosa hereditaria. The disease started eleven years ago, and the patient was treated in New York at the Skin and Cancer Hospital, with no favorable effect. I have watched the case since December 1943 and thought first of impetigo circinata serpiginosa, because the cutaneous lesions started always with a superficial impetiginous pustule, healing without a scar. In the smear staphylococci were present almost in pure culture; the intracellular and extracellular effects of the therapy with sulfathiazole internally led me to believe that it was a case of impetigo serpiginosa recidivans. Impetigo herpetiformis in women with puerperal sepsis, in pregnant women and, in some rare cases, also in men remind me very much of this eruption. I believe that one sees here a chronic superficial infection with some kind of staphyococcus which is extremely resistant. One may call this eruption "pyodermatitis superficialis serpiginosa."

DR. M. R. CARO: Was a biopsy performed?

DR. MAURICE OPPENHEIM: No.

DR. M. R. CARO: May I suggest that a biopsy be performed before anything further is done?

DR. THEODORE CORNBLEET: This man showed a typical Nikolsky sign, which occurs in familial pemphigus.

DR. MAURICE OPPENHEIM: I was never able to produce a Nikolsky sign. I do not think this eruption belongs to the pemphigus group, because it is too localized, just on the shoulders. After eleven years of duration dermatitis herpetiformis or another type of pemphigus vulgaris would show lesions in other parts of the body. The mouth is free, and the whole body except the shoulder areas is free. The lesions have always been localized in the same place.

Ocular Pemphigus. Presented by DR. E. A. OLIVER and (by invitation) DR. B. H. WEINSTEIN.

The patient, a Negro aged 46, states that in December 1942 a blister appeared on the right buccal mucosa which disappeared spontaneously in one week. He had a sore throat in February 1943. In April 1943 he had a recurrence of his sore throat and some epiphora of the right eye. The Wassermann reaction was reported negative in April 1943, but his symptoms gradually became worse, involving the mouth and throat as well as both eyes. He also complained of hoarseness at that time. In October 1943 he noticed a vesicle on his left leg, and this left an erythematous, slightly granulomatous patch. In November he noticed similar lesions on his right leg and on the scrotum. There has been a 20 pound (9.1 Kg.) loss of weight in ten months.

The Kahn reaction was negative. The urinalysis was normal, and the Frei test was slightly positive. The

hematologic examination showed 60 per cent hemoglobin, 2,970,000 erythrocytes and 3,600 leukocytes with 55 per cent polymorphonuclears, 37 per cent lymphocytes, 6 per cent eosinophils and 2 per cent basophils.

The examination shows a medium-sized Negro with decided thickening of the conjunctiva, which is spreading across the cornea in both eyes. The palpebral fissures are narrowed, and there are considerable synechiae. The larynx, buccal mucosa, pharyngeal-lingual mucosa, palate, front of the mouth and laryngeal mucosa are covered with a whitish deposit superimposed on a reddish base. On the scrotum and legs are the evidence of old bullae. The examination of the rectal mucosa shows superficial mucosal ulcerations measuring 0.5 by 1 cm.

DISCUSSION

DR. OLIVER S. ORMSBY: For at least thirty or more years I have stood up before this society and stated that there was no such thing as pemphigus of the eye. I was always convinced that patients had a sclerosing disease of the eye, but I thought that it was different from the pemphigus that occurred on the skin. In the last eight years, since Klauder and others (Klauder, J. V.: Essential Shriveling of the Conjunctiva [Ocular Pemphigus]; Pemphigus of the Mucous Membranes, ARCH. DERMAT. & SYPH. **38**:988 [Dec.] 1939. Klauder, J. V., and Cowan, A., Ocular Pemphigus and Its Relation to Pemphigus of the Skin and the Mucous Membranes, *Am. J. Ophth.* **25**:643 [June] 1942) have made convincing contributions on the subject I have changed my mind and now believe there is an ocular pemphigus. The majority of these patients have few bullae on the skin; they have most of the lesions on the tissues of the eye, and on other mucous membranes, mouth, throat and vagina. After a few years the conjunctiva becomes atrophic and sclerotic. Vision is greatly impaired or destroyed. This condition is developing in this patient. I think that this is an example of ocular pemphigus with bullae on the skin, and I think the patient's chances of getting it cleared are very limited. In the majority of cases it has been extremely resistant to treatment.

DR. LOUIS BRUNSTING, Rochester, Minn.: In early pemphigus there is no depletion of the protein in the blood and no alteration of the albumin-globulin ratio or of the electrolytes. Only in the late stages, when much of the skin has been denuded and there has been a sizable transudation of fluid, do these changes occur.

DR. EDWARD A. OLIVER: I have not much to add except to say that I feel that this is a classic example of ocular pemphigus. In addition to bullae in the inguinal region, on the leg and on the mucous membranes, proctoscopic examination reveals similar lesions in the lower part of the bowel.

Therapy was begun twelve days ago. It consists of acetarsone 0.25 Gm. three times weekly, the dose being gradually increased, and large doses of vitamin D. He has improved considerably in the last two weeks.

Angiokeratoma Corporis Diffusum (Mibelli). Presented by DR. SAMUEL J. ZAKON.

M. K., a man aged 49, born in Poland, states that he first noted the appearance of lesions about twenty-five years ago. They appear as pinhead dark brown to black spots and grow at a very slow rate. In the course of years they grow to the size of a nodule. He had suffered from varicose veins and disturbance of the peripheral vascular circulation. He received injections of sclerosing solutions in the veins and noted a decided improvement of the varicosities. A few years ago one large lesion was excised by a surgeon, and the histologic report was hemangioma. A number of the smaller lesions on the face were electrodesiccated. Some recurred. His parents and the other members of his family are still in Europe; hence he cannot state whether other members of his family suffer from a similar disease.

The examination reveals the presence of numerous discrete lesions situated on the face, arms, chest, thighs and legs. They are dark brown to dark purple and vary in size from that of a pinhead to that of a small nodule. The older lesions are elevated and have a distinctly warty appearance. The size of the lesions apparently depends on the age.

A lesion of the thigh was removed for histologic study, and the sections show blood-filled subepidermal and intraepidermal lacunas, hypertrophy of the stratum corneum and hypertrophy of the rete.

DISCUSSION

DR. UDO J. WILE, Ann Arbor, Mich.: I am extremely interested in this case. The angiokeratoma of Mibelli has up to within recent years been incorrectly described in the textbooks of dermatology as small angiomatous lesions of the scrotal sac. These have nothing whatever to do with the angiokeratoma of Mibelli, which is usually found on the extremities and is commonly due to vascular injury, particularly following frostbite. The lesions are typical. They present themselves as angiomatous lesions with atrophy and always associated with hyperkeratotic lesions.

The disease is actually a rare one, at least in this part of the country, and I believe that this is the third case that I have seen in which the diagnosis of angiokeratoma is cleancut.

DR. H. E. MICHELSON, Minneapolis: We have recently had a patient with this rare disease, and after reviewing the literature I agree with Dr. Wile that there are many cases reported in which the diagnosis is not justified. We came to the conclusion that our patient's disease was based on vascular changes, and it is my opinion that angiokeratoma should be classified as a vascular disease.

DR. S. J. ZAKON: There is a picture in Jadassohn's "Handbuch" (Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1932, vol. 12, pt. 2, p. 425) that illustrates the same type of angiokeratoma as this patient presents. The pictures in the American textbooks usually show the hands, fingers and face. This picture in Jadassohn's "Handbuch" shows the legs and trunk. The histologic section which I showed is characteristic. The young woman who makes our sections looked at the slide, opened up Kyrles's histopathology (Kyrle, J.: Vorlesungen über Histo-Biologie der menschlichen Haut und ihrer Erkrankungen, Berlin, Julius Springer, 1925, vol. 1, p. 265) and made the diagnosis before any one else, because this section is an exact duplicate of the colored picture in Kyrle's book.

Blastomycosis with Furunculoid Lesions. Presented by DR. F. E. SENEAR and DR. M. R. CARO.

A. T., a man aged 26, had pleurisy in March 1943. While he was in the hospital several small lesions developed on the left ankle. About May 1 he noticed that the left ankle had become swollen and tender. The pain increased so that weight bearing became impossible. About this time pea-sized papules appeared on both thighs and on the left buttock. These lesions gradually increased in size and became crusted.

On July 26 the patient was seen at the University of Illinois Dispensary for the first time. The left ankle

was in a cast. On each thigh and on the left buttock were quarter to half-dollar sized, crusted, violaceous plaques. On the tip of the nose there was a walnut-sized, crusted, cauliflower-like lesion with numerous tiny pustules in the periphery. The lesion had been present about four weeks.

The examination of the left ankle after the cast was removed revealed a crusted ulcer of BB shot size and a small fluctuating abscess with blueness of the overlying skin. Blastomycetes were found in pus from the lesion on the nose and in pus aspirated from the abscess on the ankle.

The microscopic examination of a biopsy specimen from the left ankle showed blastomycosis. The roentgenogram of the left ankle showed irregular areas of decalcification probably due to secondary atrophy. Roentgenographic examination of the chest showed nothing significant.

The patient has been treated with potassium iodide since the diagnosis was established. All the lesions have improved greatly. There is little discharge from the lesion on the ankle at present, and the patient is able to walk without crutches.

DISCUSSION

DR. F. E. SENEAR: I want to add a word about the patient. We saw him for the first time some months ago in another service in the hospital. At that time he had two plaques of blastomycosis on the thigh. One of the residents recovered blastomycetes. We were unable to find out what was done in the way of treatment, but those two lesions healed. He came back to us with a cast on the ankle. He had been seen in the orthopedic department, where it was thought he had a scrofulodermatous lesion on the ankle. He had at that time a typical lesion of blastomycosis on the nose, which responded well to potassium iodide. While receiving potassium iodide for this the ankle improved rapidly. When the cast was removed, we found that he had a series of four small abscesses on the ankle not resembling at all the ordinary vegetative form of blastomycosis. We were able to get a small amount of pus from one of the abscesses which was fluctuating. Blastomycetes were present in great profusion in this pus, there being about 20 or 30 to the field. I think that I have never seen a specimen in which it was easier to find the organisms.

We have seen but few cases of the furunculoid type of lesion. I had 1 other patient with a typical blastomycosis of the hand who had a lesion of cold abscess type on the flexor surface of the forearm. It was easy to recover the organisms from this abscess also. Roentgen studies of the ankle showed nothing except some rarefaction which was thought to be due to disuse of the extremity while the patient was using crutches. We have not been able to determine any systemic involvement as yet.

DR. MINNIE PERLSTEIN: The first symptom this patient had was pleurisy with effusion in which tubercle bacilli were not found.

DR. F. E. SENEAR: That pointed to the possibility of its being a tuberculous disease of the ankle.

DR. M. H. EBERT: Are these lesions similar to those seen in systemic blastomycosis?

DR. F. E. SENEAR: They are similar, and they respond to treatment. As soon as this man received treatment for the lesion on the knees, the ankles began to improve symptomatically, so that in three months he was walking without crutches and just wearing a cast. When we found so many blastomycetes we started use of potassium iodide and the lesions healed.

Morphea. Presented by DR. J. H. MITCHELL and (by invitation) DR. FRANCIS W. HETREED.

S. S., a woman aged 38, of Polish descent, first noticed changes in the skin in the lower abdominal region four and one-half months ago, which was six weeks after the delivery of her last child.

She first noticed a dollar-sized patch in the region of the right lower quadrant of the abdomen. In rather rapid succession other areas under the breast and on the sides of the abdomen developed. The most recent lesion is over the upper surface of the left scapula. Itching has been present since the onset.

On examination, there are noticed various lesions from the size of a quarter to that of a palm and hard to the touch. The initial lesion in the right lower quadrant of the abdomen has assumed a brownish color with striae gravidarum evident within the patch. Other lesions show the brownish center with the middle area normal in color, this in turn surrounded by a violaceous halo.

The skin of the head, neck and extremities is normal.

The Wassermann and Kahn reactions were negative. There were 3,900,000 erythrocytes and 6,000 leukocytes. The phosphorus level of the blood was 3.9 mg. per hundred cubic centimeters.

A Case for Diagnosis (Erythema Multiforme?). Presented by DR. THEODORE CORNBLEET and (by invitation) DR. DAVID COHEN and DR. H. C. SCHORR.

M. F., a white woman aged 30, has had an eruption on the arms and forearms for four weeks.

The lesions are grouped vesicles which dry to form scaling, erythematous, nonatrophic areas. New vesicles form about the sites; they are somewhat umbilicated and are about the size of the head of a match. New lesions continue to form after four weeks.

Three months ago the patient was hospitalized for a rectal complaint, and hemorrhoids were removed. Shortly afterward she began to have a septic type of fever. At about this time lesions developed over the tibias, which were diagnosed as erythema nodosum. These have since undergone involution. There were malaise and night sweats and then the present eruption appeared on the arms. There was a systolic murmur at the mitral area which was detected for the first time simultaneously with this last rash. The internists entertained the diagnosis of rheumatic fever. The patient has been rather uncooperative and refused to allow a biopsy to be made.

The examination of the urine gave normal results. The examination of the blood showed 4,630,000 erythrocytes, 12,000 leukocytes and 69.6 per cent hemoglobin. The differential distribution showed 53 per cent segmented forms, 36 per cent small lymphocytes, 8 per cent monocytes and 3 per cent stab cells. Culture and examination of fluid blister showed nothing noteworthy.

The stool contained blood, and Shigella alkalescens was cultured from it.

The tuberculin patch test elicited a positive reaction. The roentgenographic examination showed calcification in the right lung and paratracheal glands.

Treatment included the use of sulfadiazine, ascorbic acid and vitamin B complex.

DISCUSSION

DR. C. W. LANE, St. Louis: This patient is extremely hypochondriac, and in the case of such persons dermatitis factitia must always be considered; but the present eruption is not of a bizarre type and is present

to relatively inaccessible regions. The patient stated rather boastfully that since an operation three months ago she has been taking nine different kinds of pills and three different kinds of liquid medicine daily. With this history and the presence of a diffuse papular, vesicular, bullous, erythematous eruption, it is my opinion that this is a drug eruption, most probably due to bromides.

DR. M. H. EBERT: I am inclined to agree with Dr. Lane that this is a bromoderma. I presume it could be classified under symptomatic erythema multiforme.

DR. THEODORE CORNBLEET: We were unable to make a definite diagnosis and used a questionable erythema multiforme as a focal point for discussion. I agree that drugs may be the cause of this eruption. The patient took bromides but not recently. A bromide eruption, however, as is well known, may continue long after the drug has been taken. Since we know that the patient did take bromides the finding of them in the urine or blood does not prove the etiologic relation to the eruption. A therapeutic test with sodium chloride may be more helpful in determining this point.

A Case for Diagnosis (Pityriasis Rubra of Hebra?). Presented by DR. THEODORE CORNBLEET and (by invitation) DR. DAVID COHEN and DR. H. C. SCHORR.

M. T., a white woman aged 70, has had an eruption for eight years which began on the thighs and spread gradually to become almost universal. It consists of an erythroderma with fine branny scaling. There is little itching. On the back are what appear to be normal areas of skin as small island insets. There is a diffuse atrophy of the forehead, cheeks, forearms and legs. There is slight involvement of the palms and more of the soles. The toe nails are hyperkeratotic and raised above their beds by debris. The finger nails are striated. The lips and tongue are atrophic, with the latter displaying a purplish cast.

The hematologic studies, which included serum tests for syphilis, cells counts, differential counts and chemical examinations, all gave normal results. There was nothing abnormal about the urine. Tests indicated that hepatic function was satisfactory. The vitamin A concentration was 14 micrograms per hundred cubic centimeters of blood and the carotene concentration 55 micrograms. Roentgenographic examination of the chest showed nothing abnormal.

Histologic examination showed a thin scale with islands of parakeratosis and an epidermis which in parts was flattened. The granular layer was discontinuous; there was a slight intercellular edema throughout the epidermis, and the basal layer was intact, although it showed ballooning of many cells. In the upper part of the corium there was a well defined horizontal band in which lay many densely packed foci composed of dilated and engorged blood vessels surrounded by lymphocytes, lymphoblasts, histiocytes and chromatophores filled with granules of melanin. The elastic fibers were thinned and fragmented in the zones of the infiltrate but were not entirely destroyed.

DISCUSSION

DR. HERBERT RATTNER: It was my impression that this patient had a scaly erythroderma on a senile skin. Perhaps later it will be possible to establish other evidence of lymphoblastoma.

DR. MAURICE OPPENHEIM (by invitation): It may be dermatitis herpetiformis superimposed on dermatitis atrophicans. The histologic features indicate dermatitis atrophicans.

DR. F. W. LYNCH, St. Paul: I agree with Dr. Rattner's impression as to the presence of atrophy. The eruption has some resemblance to the poikiloderma-like changes described by Lane and others in association with certain instances of lymphoblastoma. A somewhat similar case was described by Hazel in 1939 (Hazel, O. G.: Poikiloderma Atrophicans Vasculare: Report of a Case with a Review of the Recent Literature, ARCH. DERMAT. & SYPH. **40**:276 [Nov.] 1939).

DR. THEODORE CORNBLEET: We thought of pityriasis rubra of Hebra, but there are several arguments against that diagnosis. Atrophy is an integral part of Hebra's entity but is lacking over the greater part of the present eruption. Pigmentation, too, is a feature necessary for such a diagnosis but is not present here. Pityriasis rubra of Hebra has been shown latterly to eventuate into a frank lymphoblastoma rather than the tuberculosis previously observed by writers. We naturally are watching for a leukemic or related outcome. In the meantime we favor another possibility. It was undoubtedly noticed that this patient had a low level of vitamin A in her blood, namely 1.4 micrograms per hundred cubic centimeters. This is definitely in the pathologic range. The erythroderma, ectropion and other changes are not unlike what may be expected in pityriasis rubra pilaris. Others as well as we have found low vitamin A values in the latter disease; hence the values found in this case are confirmatory of such a diagnosis. This woman showed something else in support of this, that is, the few normal islands of skin within the sea of erythroderma.

Xanthomatosis with Tendon Xanthomas. Presented (by invitation) by DR. S. ROTHMAN and DR. A. B. HENNINGSEN.

The patient, a 28 year old white woman, was admitted to the department of surgery of Albert Merritt Billings Hospital on Oct. 27, 1943, with signs similar to those now present. The first lesion appeared six years ago on the dorsum of the right hand. The other lesions have gradually developed in the last three years. The tendon lesions have all been growing during the past year. There have been muscle pain, migrating joint pain and stiffness for one year.

Gastrointestinal symptoms consisting of belching, nausea, pain of the abdomen in the right upper quadrant and distention of one year's duration pointed to the possibility of gastrointestinal involvement and cholesterol stone formation in the biliary system. A cholecystogram, however, was normal.

The patient's mother had similar lesions on the eyelids, over the knuckles and on the achilles tendons. No other relatives are known to have been affected.

There are firm hard nodules covered by normal skin over the right olecranon process, also tumors obviously attached to the extensor tendon sheaths over the second and third metacarpophalangeal joints of both hands and multiple nodules in the patellar and achilles tendons bilaterally, over which the skin is movable. A cutaneous xanthoma is present adjacent to the medial canthus of the left eye.

The laboratory examination revealed the following values for lipids in the blood:

Date	Total Lipids, Mg./100 Cc.	Total Cholesterol, Mg./100 Cc.	Free Cholesterol, Mg./100 Cc.
10/28/43	1,577	430	320
11/22/43	1,602	430	258
12/23/43	1,620	...	...
1/ 7/44	.....	210	151.3
1/17/44	.....	231	152.7

Other laboratory examinations, including blood counts, urinalysis, determination of the Kahn reaction and roentgenographic examination of the chest, skull and bones of the right hand and right ankle, revealed no abnormalities.

The condition of the patient was not essentially influenced by a low cholesterol diet. The recent improvement of the blood cholesterol level may be due to the administration of lipocaic (26 capsules per day for several weeks and 18 capsules more recently) over a period of three months.

Histologic examination showed typical xanthoma structure.

DISCUSSION

DR. ARTHUR C. CURTIS, Ann Arbor, Mich.: This case was interesting to me because it emphasized one thing that Dr. Hamilton Montgomery has emphasized, the frequent incidence of cardiovascular disease in a patient with xanthomatosis. This patient's mother died at 52 of coronary occlusion. She said that her mother's family was "filled with cardiovascular disease." In addition to the xanthomas of the tendons she had a xanthelasma on the eyelid. We have made studies of the blood fat of 39 patients who have xanthoma palpebrarum. Eight receiving 15 Gm. of lecithin daily were followed for from forty-six to one-hundred and eighty-nine days. Unfortunately these patients have had no changes in the xanthelasma lesions or any fall in blood fat levels.

DR. S. ROTHMAN (by invitation): The blood lipid values have come closer to normal since the patient has been given lipocaic, a pancreatic substance which was isolated by Dr. L. R. Dragstedt at the University of Chicago.

Disseminated Lupus Erythematosus. Presented by DR. J. H. MITCHELL, DR. R. H. SCULL and (by invitation) DR. FRANCIS W. HETREED.

J. B., a woman aged 48, of Irish descent, first had an eruption on her nose twenty-five years ago. It spread gradually to involve both cheeks and the chin. Three years ago the lesions appeared on the hands and arms, but they subsequently disappeared. They recurred on the hands three months ago and now are spreading up both arms. The lesions about the mouth and chin healed with atrophy.

Her husband is living, as well as two children, 25 and 18 years old. There were two miscarriages, about seventeen years ago.

Examination shows practically complete involvement of the nose, both cheeks and chin. The lesions are erythematous, scaling, keratotic and grouped. On diascopic pressure a few small brownish nodules are seen. The extensor surface of both arms and forearms show erythematous slightly scaling lesions. The dorsal surface of hands and fingers show lesions with a relative freedom of the middle phalanges, especially on the right side.

The temperature was normal. Examination of the blood showed 4,500,000 erythrocytes and 8,200 leukocytes. The Wassermann and Kahn reactions were negative. The differential count showed 65 per cent neutrophils, 30 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils.

DISCUSSION

DR. ARTHUR C. CURTIS, Ann Arbor, Mich.: I agree with the diagnosis of lupus erythematosus. I think it interesting, in view of some of the recent work that has been done in a similar disease, that is, periarteritis nodosa, that many features of lupus erythematosus and periarteritis nodosa are the same. There has recently been reported, in the *Archives of Pathology*, a case of lupus erythematosus in which the clinical history pointed to an allergic cause for the disease. We have recently studied a patient in the University Hospital by determination of the leukopenic index after exposure to ultraviolet irradiation. The leukocytes fell from 6,500 to 3,000 and then, with the development of the erythema, went to 9,500 and then fell to the normal level in a twenty-four hour period. This type of reaction suggests a definite allergic reaction, in this case to light.

DR. H. E. MICHELSON: Minneapolis: I cannot let this case go by without asking either Dr. O'Leary or Dr. Brunsting to tell us on what symptoms they base their prognosis in cases of acute lupus erythematosus. When these patients complain of great fatigue, it means considerable to me.

DR. PAUL A. O'LEARY, Rochester, Minn.: The diagnosis of chronic disseminated lupus erythematosus seems warranted in this case. For several patients we recently made the diagnosis of disseminated lupus erythematosus before they manifested the cutaneous signs of the disease. In young women who complain of pains in joints without roentgen evidence of bony changes, a mild degree of fever, a high sedimentation rate and a leukopenia, a diagnosis of acute or subacute disseminated lupus erythematosus is usually warranted, even though there are no lesions present.

DR. LOUIS BRUNSTING, Rochester, Minn.: I should like to emphasize some points in dealing with the early phases of disseminated lupus erythematosus and also the differentiation of the disease from dermatomyositis. It is well known that young women are particularly affected and that for a number of months before onset of the eruption there may be vague complaints such as malaise, fatigue and, particularly, transient arthralgias. The laboratory analyses often show secondary anemia, leukopenia, an increased sedimentation rate of the erythrocytes and sometimes albuminuria. In such patients, under provocation of sunlight, infection or some other mechanism, the cutaneous signs may first appear. The reaction of the patient seems to be out of proportion to the insult, as though the person had been sensitized by some previous episode, and in the history of these cases I believe emphasis should be laid on the search for past infections, particularly those of the streptococcic group, such as rheumatic fever and chorea. There are similarities among the syndromes of disseminated lupus erythematosus, subacute bacterial endocarditis and periarteritis nodosa.

In dermatomyositis the patient may be an adult or a child and the first complaints have to do with tenderness and stiffness of the muscles rather than the joints. There may be edema of the face and extremities and a suffusion of the skin over the face and neck of a violaceous hue; the so-called heliotrope eyelids are distinctive. There may be violaceous scaling plaques over the knuckles, elbows and knees as the earliest signs of the eruption. Usually there is no leukopenia or elevation of the sedimentation rate unless there is fever, but a consistent abnormality is noted in the form of creatininuria, which waxes and wanes in the various stages of the disease. This seems to be an end result of the degenerative changes which occur in the muscles, the reaction of which can be demonstrated by biopsy.

DR. STEPHAN EPSTEIN, Marshfield, Wis.: I agree with Dr. O'Leary that this is the chronic type of disseminated lupus erythematosus. I thought that the lesions in this woman were also interesting from a morphologic point of view. This patient has definite lesions at the tips of the fingers. Usually one considers these lesions as an indication of the subacute or acute form. In this case the patient does not present signs of a subacute eruption. If one looks closely at the eruption of the fingers it will be seen they are a little different from the erythematous lesions which are usually found in this location. This patient shows definite tiny hyperkeratoses and telangiectases at the terminal phalanges of the fingers. This picture corresponds to the lesions in chronic lupus erythematosus and seems to be rare. I remember only 1 other case in which I have seen similar lesions on the fingers.

DR. M. H. EBERT: Clinically I thought those lesions on the fingers were interesting. It looks as though they had been originally punched out. They were suggestive of a syphilitic lesion. The patient also had a lesion with punched-out appearance on the nose, which would indicate a destructive action suggestive of lupus vulgaris. I think that without lesions on the hands and arms and no biopsy this would have been an interesting differential diagnosis from a clinical point of view.

I thought that this was an interesting case from two or three angles, the first of which was the possibility that syphilis is present. That is of clinical significance in early acute lupus erythematosus. Fifteen or twenty years ago I presented a patient with acute lupus erythematosus with lesions on the finger tips.

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Feb. 1, 1944

A Case for Diagnosis (Psoriasis?). Presented by DR. E. W. ABRAMOWITZ.

C. S., a woman aged 62, was previously presented at the New York Academy of Medicine, Section of Dermatology and Syphilis, on Jan. 4, 1944.

Biopsy of a lesion on the left elbow was reported as indicative of psoriasis, while biopsy of a lesion on the face was reported as indicating lupus erythematosus. The results of a urinalysis were normal, and the Wassermann reaction of the blood was negative.

The patient has received numerous injections of liver extract and injections of bismuth subsalicylate without benefit. Since the application of ammoniated mercury and salicylic acid ointment to the eruption on the face, the eruption has improved considerably.

DISCUSSION

DR. E. W. ABRAMOWITZ: This patient was presented in January 1944 on account of the eruption on the face which closely resembled lupus erythematosus. However, she had some lesions on the elbows and one lesion on a buttock which looked more like psoriasis. The eruption was of comparatively short duration, and she gave a history of having had a similar outbreak about four or five years previously; it had disappeared after a few injections of a bismuth preparation. The histopathologic examination of the lesion on the face was reported as indicating lupus erythematosus. I believe that I said at that time that I was not sure whether she had lupus erythematosus of the face and psoriasis of the body or whether it was psoriasis in both areas. With use of ammoniated mercury and salicylic acid ointment the eruption on the face is less conspicuous. I believe that there was a biopsy from the lesion on the body, which showed psoriasis. Dr. Sachs still insists that the histologic picture of the lesion on the face is typical of lupus erythematosus. Nevertheless, I believe now that the whole eruption is psoriasis. Dr. Rosen concurs in this opinion.

DR. ISADORE ROSEN: This case illustrates the fallacy of making a diagnosis of lupus erythematosus just because the patient has symmetric lesions on the face. Psoriasis limited to the face is sometimes mistaken for lupus erythematosus. In this particular patient there were one or two lesions of psoriasis on the trunk, a fact which helps in differential diagnosis.

DR. LOUIS CHARGIN: If this patient did not have an eruption on the body I wonder whether it would be so easy to make the diagnosis of psoriasis. I cannot make a diagnosis in this case. I do not know what the lesion on the face is. There are some points in favor of lupus erythematosus and some in favor of psoriasis. Likewise it lacks some of the essentials of each. A positive diagnosis of psoriasis is difficult to make if one examines the lesions on the face. One should try if possible to fit all the lesions into one disease entity. From the appearance of the lesions on the arm, one would make a diagnosis of psoriasis. I think that perhaps another biopsy might clear up the difficulty, since the pathologist has made the diagnosis of lupus erythematosus.

DR. PAUL GROSS: The statement by Dr. Rosen that the location of dermatologic lesions should not be a criterion in making a diagnosis deserves special indorsement in this case. On the other hand, the presence of psoriatic lesions on the body does not exclude the possibility that the facial eruption is lupus erythematosus. To settle the question, the eruption on the face should be further treated with topical applications suitable for psoriasis. If there is no response, another biopsy will be necessary to confirm the diagnosis of lupus erythematosus.

DR. OSCAR L. LEVIN: I cannot make a positive diagnosis on this examination. However, from examination of the lesions, certain diseases are suggested. First, on the face, seborrheic dermatitis, which I do not think it is, comes under consideration because of the distribution and other factors. Psoriasis resembles it. It also suggests lupus erythematosus, but the usual characteristics are absent. The eruption of the face, if seen alone, makes one think of avitaminosis. I do not know whether the patient suffers from avitaminosis, but I should like to try large doses of vitamin B complex, riboflavin especially. The lesion on the back of the left elbow suggests psoriasis. It could be psoriasis, but I do not think that it is, because the patch is made up of pinhead-sized and slightly larger, elevated papules of a reddish color on an inflammatory base and the scaling is not that of psoriasis. There are not the bleeding points of psoriasis. Clinically I do not believe the papules are those of psoriasis. Lupus erythematosus is readily excluded. The report on the pathologic change of the lesion on the elbow I believe indicates psoriasis.

The patch on the left buttock is fairly sharply circumscribed, not so red as the lesion on the face but slightly darker than that on the elbow and shows none

of the characteristics of lupus erythematosus and none of the signs of psoriasis. If I were required to make a diagnosis to explain the whole picture, I should make a diagnosis of erythroderma and small miliary sarcoid of Boeck. This should be confirmed by a negative reaction to tuberculin and the results of further study of the pathologic conditions.

DR. E. W. ABRAMOWITZ: Some authorities say that the histologic picture of lupus erythematosus is not definite. Pathologists once in a while report eruptions of lichen planus and other dermatoses as lupus erythematosus, and they report lupus erythematosus as other dermatosus. If this is lupus erythematosus of the face, it certainly has developed rapidly in the short time the patient has had the eruption. She has an isolated patch on the buttock and patches on the elbows that apparently are psoriasis. She has no lesions on the scalp or elsewhere on the body to help in the diagnosis of psoriasis.

DR. DAVID BLOOM: Frequent observation of the patient made me change the diagnosis from lupus erythematosus to psoriasis. Injections of a bismuth preparation and of liver extract were of no benefit, but the eruption responded remarkably to the application of ammoniated mercury and salicylic acid ointment.

A Case for Diagnosis (Ephedrine Eruption? Lichen Planus?). Presented by DR. E. W. ABRAMOWITZ.

W. J., a woman aged 71, was previously presented at the Manhattan Dermatological Society, on Jan. 11, 1944, although the case was not included in the published transactions of the society.

The patient was first seen at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Dec. 27, 1943, complaining of an eruption of three months' duration. From October 27 to December 20, she had been receiving from a private physician drops containing zinc sulfate, and ephedrine, for an inflammation of the eyes. About one month after she started to use the drops, the eruption appeared on her face and later extended to the upper extremities.

The face shows symmetrically a fairly well defined, brownish red plaque, and a similar plaque is seen on the left buttock. On the extensor surfaces of the upper extremities, there is a papular eruption of bluish red color.

A patch test with the eye drops elicited a negative reaction. Urinalysis gave normal results. The Wassermann reaction of the blood was negative. The blood count was normal. Biopsy of a specimen taken from a lesion on the back of the forearm was reported as showing a toxic dermatitis (possibly drug eruption).

DISCUSSION

DR. E. W. ABRAMOWITZ: This is another case which has presented difficulties from the standpoint of clinical diagnosis. The patient was presented previously at the Manhattan Dermatological Society as possibly having a drug eruption due to ephedrine. She had been using drops containing that drug. The eruption was much more conspicuous on the face at that time than it is now. On the arms it was about the same as it is at present. The impression that one gets on examining the patient's arms now without looking at the face is that she has acute lichen planus, even though it is distributed on the extensor surfaces. She has no itching, and there are no lesions in the mouth. A biopsy was made from one of the lesions on the arm. There was no histologic picture of lichen planus, only a rather uniform plasma cell infiltration in the upper part of the corium with some changes in the blood vessels and nothing else. Dr. Sachs came to the final conclusion that the best diagnosis he could offer was some sort of toxic eruption due to a drug. The eruption on the face is clearing. It has left behind considerable pigmentation. The few scattered lesions on the body are clearing, but the eruption on the arms has remained about the same except that some of the papules have a linear arrangement. There are a few that show an annular arrangement. Some of my associates and I feel that it is not a classic lichen planus. I have seen eruptions of this type that defy definite classification for some time until finally the patient begins to show manifestations of Hodgkins' disease or of some other type of lymphoblastoma.

DR. ISADORE ROSEN: I think that the lesions on the face and upper extremities are of the same causation. My clinical diagnosis is toxic erythema now in the process of repair. When I first saw this patient at the clinic, the features were much more characteristic of a toxic eruption than they are this evening.

DR. G. F. MACHACEK: From what I saw I should say that this is not lichen planus but some more deeply seated, inflammatory, tiny granulomatous infiltration. I did not study it in its finer details. I suggest investigation from the standpoint of the cholesterol content of the blood. It is possibly xanthoma diabeticorum. I have seen such lesions which did not look much different under the microscope.

DR. EUGENE TRAUGOTT BERNSTEIN: On the ground of the morphologic attributes I should exclude lichen planus. There is no umbilication. The single lesions do not show polygonal outlines. The symmetric distribution on the extremities, the raised lesions and the distribution on the face and extremities together show the picture seen in erythema multiforme of toxic origin. I agree with the others that this is a toxic eruption, but there is one feature which is striking, the patch on the buttocks with pigmentation to an extent which impresses me as poikiloderma vasculare (Civatte), as seen on the anterior aspect of the neck and chest. I think that the clinical appearance is not at all like that of lichen planus, and the diagnosis of a toxic eruption should be accepted.

DR. MABEL SILVERBERG: The patient had all her teeth extracted on one day and the eruption appeared not long afterward. I think that that sort of trauma can cause this type of eruption.

DR. E. W. ABRAMOWITZ: The eruption did not fit into any group of sarcoid even though it might turn out to be some form of tuberculid. There have been a good many diagnoses suggested. As for toxic eruption from a drug, of course I know that ephedrine produces many kinds of eruptions, as do other drugs for that matter. The patient has not had any other medicine, like arsenic, that I know of. That type of eruption after arsenic might persist for such a length of time, but still it would not give an almost pure plasma cell infiltration which this section shows. We are trying to make some hematologic studies to see if they will help in making the diagnosis. The patient has not been fully cooperative.

Exfoliative Dermatitis. Presented by DR. CHARLES WOLF.

H. P., a Negro boy aged 10, states that in April, 1943, a scaliness first appeared on the scalp and was followed within a week by a generalized eruption con-

sting of pinhead-sized erythematous papules. Within short time the eruption changed into an erythrodermic caly dermatitis. There is a generalized erythroderma ith a fine desquamating scale and involvement of the les and palms as well as the nails.

Examination of the urine for arsenic showed a slight race. The Wassermann reaction was negative. A ematologic examination showed 70 per cent hemoglobin, 3,500,000 erythrocytes and 3,888 leukocytes.

DISCUSSION

DR. PAUL GROSS: This boy has a generalized erythroderma, to give the eruption a descriptive name. The teresting features are scaling of the scalp, hyperkeratosis of the palms and soles and a somewhat rough ppearance of the erythematous skin. For this reason believe that this is a pityriasis-rubra-pilaris-like eruption as occasionally observed in children. I have found hat this dermatosis responds to parenteral injection f liver preparations and oral administration of vitamin A.

DR. OSCAR L. LEVIN: I think that this eruption is due to ingestion of arsenic. The patient has an almost universal erythema with inflammatory changes and secondary exfoliation. For treatment I advise plenty of fluids, rest, the search for and exclusion of arsenic ingestion and the use of a bland ointment for the skin. It will take months to cure the eruption. I think, in an individual of this age with a generalized eruption of this type, arsenic dermatitis should be excluded.

DR. LOUIS CHARGIN: I cannot offer a diagnosis in this case but I should like to second the views of Dr. Gross that we are perhaps dealing here with the so-called pityriasis rubra pilaris. I have seen this in younger children. I recall a child of 4 years with a similar eruption which was not true pityriasis rubra pilaris but presented a picture much like it. The therapeutic suggestions made by Dr. Gross are good, but if they are left alone these patients get well.

DR. OSCAR L. LEVIN: On what grounds is the diagnosis of pityriasis rubra pilaris made?

DR. PAUL GROSS: As I said before, this is an erythroderma and there is no extensive exfoliation present. There is rather an accentuation of the follicles. In the absence of typical follicular plugging on the dorsum of the fingers, I prefer to call this condition a pityriasis-rubra-pilaris-like eruption rather than pityriasis rubra pilaris. If, as Dr. Chargin said, a patient like this may get well in the hospital without vitamin therapy, then this is due to an improvement in nutrition. The same holds true for typical vitamin deficiencies, provided they have not progressed too far.

DR. DAVID BLOOM: I favor the diagnosis of pityriasis rubra pilaris. If the patient had had a few follicular keratotic papules on the backs of his fingers, hardly any one would have disputed this diagnosis.

DR. CHARLES WOLF: I want to disillusion any one who thinks this is pityriasis rubra pilaris. While in the hospital he received good medical care and became worse. There was no involvement of the hair follicles at any time. It was a papular eruption in the interfollicular spaces. Perhaps pityriasis rubra of Hebra may be considered. To sum up, I think this is a case of exfoliative dermatitis of the Brock-Wilson type. Whether ingestion of chemicals is an etiologic factor in this case one cannot definitely state.

DR. PAUL GROSS: After the rather vehement expression of opinion by Dr. Wolf, I believe this patient should be presented again after he has received treatment with liver and vitamin A.

Erythroderma Ichthyosiforme Congenitale. Presented by DR. ISADORE ROSEN.

A. R., a man aged 22, was admitted to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Dec. 13, 1943, with an eruption on the body which has been present since birth. The skin on the trunk and extremities is considerably thickened, dry and scaly. The lower part of the back and the lower two thirds of the trunk anteriorly show much more intense involvement than the upper third of the trunk. The palms and soles are hyperkeratotic. The nails are thickened. The scalp is dry and scaly.

The patient's two brothers and one sister are normal. Neither of the parents has an abnormal skin. The parents are not related to each other. The patient states that he does not perspire at all except on the face and scalp. He feels, therefore, extremely uncomfortable in the summer.

The urine was normal. The Wassermann reaction was negative. Microscopic examination showed considerable hyperkeratosis, considerable acanthosis and moderate cellular infiltration in the upper part of the cutis.

DISCUSSION

DR. ADOLPH ROSTENBERG: While I fully agree with Dr. Rosen, there are some features missing. A striking feature in a patient of mine, an 18 year old woman, was redness of the face; it was extremely red and congested, and the ichthyotic condition was more in plaque form, distributed on the extremities. Yet, I suppose the disease is so rare that one does not see the same features in every case.

Dr. E. W. Abramowitz, Dr. Max Scheer and Dr. Oscar L. Levin agreed with the diagnosis as presented.

Correspondence

PREVENTION OF IMMEDIATE NAUSEA AND VOMITING FOLLOWING ADMINISTRATION OF NEOARSPHENAMINE

To the Editor:—During my experience at the Erlanger Hospital Venereal Disease Clinic, in Chattanooga, Tenn., with many hundreds of patients being treated for syphilis, I found that many complained of nausea and vomiting immediately after the intravenous injection of neoarsphenamine. The nausea and vomiting were severe enough to deter them from continuing their treatments, with the result that there were many delinquents because of this reaction. Most of these patients continued to have nausea and vomiting even after mapharsen was substituted for neoarsphenamine.

I interrogated the reacting patients regarding their symptoms, and they all agreed that the nausea and vomiting were caused by the odor and taste of the drug immediately after the start of the injection and before it was completed.

Several different measures were tried to control this, like chewing gum, smoking a cigaret, pinching the nostrils together, smelling perfume from a handkerchief to the nose while the injection was being given, abstaining from food for two hours before the injection and others. None of these measures were effective.

I concluded that if I could temporarily anesthetize the taste buds on the tongue, and thus abolish taste sensation, it would prevent reflex nausea and vomiting. I tried this with the patients who were routinely assigned to me and who complained of nausea and vomiting.

Before these patients received their intravenous injection, I gave them 2 tablets containing ethyl aminobenzoate (¼ grain [0.015 Gm.] each) with instructions to place both tablets on the tongue and to keep them on the tongue until the tablets were dissolved. After treatment, they reported back to me before leaving the clinic. In each instance I was informed by a smiling and grateful patient that there was no nausea or vomiting. The vomiting patients refused to take their subsequent treatments without seeing me first and obtaining the tablets. I treated several hundred patients with these tablets, with success in every case, surprising as it may seem.

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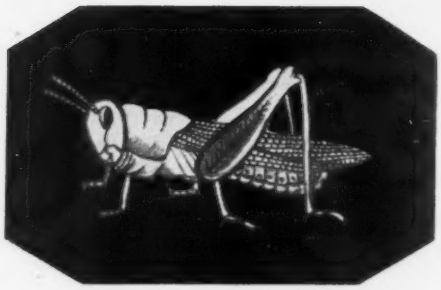

Tithonus

IT IS told that Aurora, goddess of the Dawn became enamoured with a mortal, the beautiful, young Tithonus and married him. As the years passed, to her great mortification the hair of Tithonus grew thin and gray, and his steps tottering. Unable longer to bear the sight, Aurora in desperation, turned him into a grasshopper. Blame the god Jupiter for the whole thing; he had granted him immortality as a wedding gift but forgot to include perpetual youth. We are not told what strange things this poor man did to fight off the appearance of age but can well imagine. Someone forgot to tell him that cleanliness is akin to godliness, and of all things used to clean the skin CREAM OF SOAP* approaches close to the ideal.

* * *

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3. Its pH of 6.25 is compatible with that of the skin.

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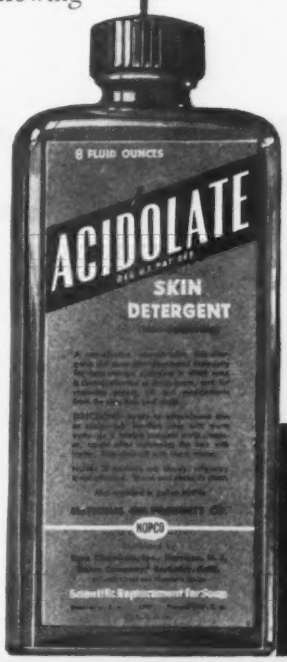

Literature and sample to physicians on request

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*Acidolate is a trademark of National Oil Products Co.

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